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=> s acetic acid(10a)lyophil?(10a)peptide and (bombesin or protirelin or somatostatin
or cetrorelix)
        115920 ACETIC
        391843 ACID
        102715 ACETIC ACID
                 (ACETIC(W)ACID)
         19118 LYOPHIL?
         17043 PEPTIDE
           398 ACETIC ACID(10A)LYOPHIL?(10A)PEPTIDE
           194 BOMBESIN
            13 PROTIRELIN
          1017 SOMATOSTATIN
             4 CETRORELIX
L1           45 ACETIC ACID(10A)LYOPHIL?(10A)PEPTIDE AND (BOMBESIN OR PROTI
REL
               IN OR SOMATOSTATIN OR CETRORELIX)

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US PAT NO:      5,574,008 [IMAGE AVAILABLE]            L1: 1 of 45
DATE ISSUED:    Nov. 12, 1996
TITLE:          Biologically active fragments of glucagon-like
                  insulinotropic peptide
INVENTOR:       William T. Johnson, Indianapolis, IN
                Fatima E. Yakubu-Madas, Indianapolis, IN
ASSIGNEE:       Eli Lilly and Company, Indianapolis, IN (U.S. corp.)
APPL-NO:        08/297,731
DATE FILED:     Aug. 30, 1994
ART-UNIT:       182
PRIM-EXMR:      Marianne P. Allen
LEGAL-REP:      Ronald S. Maciak, David E. Boone

US PAT NO:      5,574,008 [IMAGE AVAILABLE]            L1: 1 of 45

ABSTRACT:
N-terminal truncated forms of glucagon like insulinotropic peptide
(GLP-1) and analogs thereof are provided. The claimed polypeptides
promote glucose uptake by cells but do not stimulate insulin expression
or secretion. The invention also provides methods for treating diabetes
```

and pharmaceutical formulations comprising the claimed polypeptides.

SUMMARY:

BSUM(4)

Endocrine . . . as glucose, amino acids, and catecholamines, but also by local paracrine influences. The major pancreatic islet hormones, glucagon, insulin and **somatostatin**, interact with specific pancreatic cell types (A, B, and D cells, respectively) to modulate the secretory response. Although insulin secretion is predominantly controlled by blood glucose levels, **somatostatin** inhibits glucose-mediated insulin secretion.

SUMMARY:

BSUM(43)

Boc . . . followed by thirty minutes at 0.degree. C. After removal of the HF, the peptide/resin is washed with ether, and the **peptide** extracted with glacial **acetic** **acid** and **lyophilized**.

US PAT NO: 5,512,549 [IMAGE AVAILABLE] L1: 2 of 45
DATE ISSUED: Apr. 30, 1996
TITLE: Glucagon-like insulinotropic peptide analogs, compositions, and methods of use
INVENTOR: Victor J. Chen, Indianapolis, IN
Richard D. DiMarchi, Carmel, IN
David L. Smiley, Greenfield, IN
Russell D. Stucky, Indianapolis, IN
Aidas V. Kriauciunas, Indianapolis, IN
ASSIGNEE: Eli Lilly and Company, Indianapolis, IN (U.S. corp.)
APPL-NO: 08/324,960
DATE FILED: Oct. 18, 1994
ART-UNIT: 181
PRIM-EXMR: Jill Warden
ASST-EXMR: Benet Prickril
LEGAL-REP: Ronald S. Maciak, David E. Boone

US PAT NO: 5,512,549 [IMAGE AVAILABLE] L1: 2 of 45

ABSTRACT:
Glucagon-like insulinotropic peptide (GLP-1(7-37)) analogs and derivatives are disclosed. The analogs include amino acid substitutions, amino and carboxyl terminal modifications, and C.sub.6 -C.sub.10 acylations. The claimed compounds stimulate the secretion or biosynthesis of insulin in poorly functioning beta cells and are therefore useful in treating Type II diabetics

SUMMARY:

BSUM(4)

Endocrine . . . as glucose, amino acids, and catecholamines, but also by local paracrine influences. The major pancreatic islet hormones, glucagon, insulin and **somatostatin**, interact with specific pancreatic

cell types (A, B, and D cells, respectively) to modulate the secretory response. Although insulin secretion is predominantly controlled by blood glucose levels, **somatostatin** inhibits glucose-mediated insulin secretion. In addition to inter-islet paracrine regulation of insulin secretion, there is evidence to support the existence. . .

SUMMARY:

BSUM(36)

Boc . . . C., preferably on ice for 60 minutes. After removal of the HF, the peptide/resin is washed with ether, and the **peptide** extracted with glacial **acetic** **acid** and **lyophilized**.

US PAT NO: 5,480,869 [IMAGE AVAILABLE] L1: 3 of 45
DATE ISSUED: Jan. 2, 1996
TITLE: Anti-inflammatory peptide analogs and treatment to inhibit vascular leakage in injured tissues
INVENTOR: Edward T. Wei, Berkeley, CA
Holly A. Thomas, Wilmette, IL
ASSIGNEE: The Regents of the University of California, Oakland, CA (U.S. corp.)
APPL-NO: 08/096,724
DATE FILED: Jul. 23, 1993
ART-UNIT: 181
PRIM-EXMR: Jill Warden
ASST-EXMR: A. M. Davenport
LEGAL-REP: Majestic, Parsons, Siebert & Hsue

US PAT NO: 5,480,869 [IMAGE AVAILABLE] L1: 3 of 45

ABSTRACT:
Small, anti-inflammatory compounds that are peptide analogs are described useful to inhibit inflammation of a mammal's skin, mucous membranes, or lacerations of the musculature or injury to the brain or leakage of fluids into the air spaces of the lungs. Peptide analogs of the invention have the primary sequence T.sub.N -A.sub.1 -A.sub.2 -A.sub.3 -A.sub.4 -A.sub.5 -A.sub.6 -T.sub.C where one of the moieties is in the D-configuration. A.sub.1 and A.sub.2 are each a basic polar amino acids while each of A.sub.3, A.sub.4, and A.sub.6 is a hydrophobic amino acid. A.sub.5 can be a variety of structures and appears to function to optimize the spatial relationship between the hydrophobic and the basic residues. T.sub.N is selected or modified to convey resistance against enzymatic degradation. T.sub.C is an amino group or an amidated amino acid, preferably hydrophobic.

SUMMARY:

BSUM(37)

Nocifensive . . . bonds. The approach of replacing the peptide bond with a reduced bond has been used in developing antagonists for gastrin, **bombesin**, substance P, and secretin, and for neurotensin analogs.) The amino terminal, or T.sub.N, has a molecular weight less than about. . .

SUMMARY:

BSUM(51)

HF . . . precedes multiple washes of the peptide-resin with dry ethyl ether and/or chloroform for extraction. Filtration follows with one molar aqueous **acetic** **acid**, with the obtained filtrate frozen and **lyophilized**. The used resin is weighed to determine the yield of **peptide**, and the need for any re-extraction. Finally, the synthesized peptides are purified by ion-exchange chromatography and by preparative HPLC. The. . .

US PAT NO: 5,480,868 [IMAGE AVAILABLE] L1: 4 of 45
DATE ISSUED: Jan. 2, 1996
TITLE: Sustained-release preparation
INVENTOR: Shigeru Kamei, Takarazuka, Japan
Yasutaka Igari, Kobe, Japan
Yasuaki Ogawa, Ohyamazaki, Japan
ASSIGNEE: Takeda Chemical Industries, ltd., Osaka, Japan (foreign corp.)
APPL-NO: 08/162,698
DATE FILED: Dec. 7, 1993
ART-UNIT: 181
PRIM-EXMR: Jill Warden
ASST-EXMR: Shella J. Huff
LEGAL-REP: Foley & Lardner

US PAT NO: 5,480,868 [IMAGE AVAILABLE] L1: 4 of 45

ABSTRACT:
A sustained-release preparation which comprises a physiologically active peptide of general formula ##STR1## wherein X represents an acyl group; R.sub.1, R.sub.2 and R.sub.4 each represents an aromatic cyclic group; R.sub.3 represents a D-amino acid residue or a group of the formula ##STR2## wherein R.sub.3 ' is a heterocyclic group; R.sub.5 represents a group of the formula --(CH.sub.2).sub.n --R.sub.5 ' wherein n is 2 or 3, and R.sub.5 ' is an amino group which may optionally be substituted, an aromatic cyclic group or an O-glycosyl group;
R.sub.6 represents a group of the formula --(CH.sub.2).sub.n --R.sub.6 ' wherein n is 2 or 3, and R.sub.6 ' is an amino group which may optionally be substituted;
R.sub.7 represents a D-amino acid residue or an azaglycyl residue; and
Q represents hydrogen or a lower alkyl group, or a salt thereof and a biodegradable polymer having a terminal carboxyl group.
The sustained-release preparation shows a constant release of the peptide over a long time and is substantially free from an initial burst.

SUMMARY:

BSUM(122)

As . . . may be mentioned luteinizing hormone releasing hormone (LH-RH) antagonists (cf. U.S. Pat. Nos. 4,086,219, 4,124,577, 4,253,997 and 4,317,815, etc.), insulin, **somatostatin**, **somatostatin** derivatives (cf. U.S. Pat. Nos. 4,087,390, 4,093,574, 4,100,117, 4,253,998, etc.), growth hormone, prolactin, adrenocorticotropic hormone

(ACTH), melanocyte stimulating hormone (MSH),. . . its derivatives (cf. U.S. Pat. No. 4,229,438), other thymic factors, tumor necrosis factor (TNF), colony stimulating factor (CSF), motilin, dynorphin, **bombesin**, neurotensin, cerulein, bradykinin, atrial natruretic factor, nerve growth factor, cell growth factor, neurotrophic factor, peptides having endothelin antagonistic activity (cf.. . .

DETDESC:

DETD(63)

After . . . thus-obtained resin was first washed with ether, then stirred at room temperature for 15 minutes in 50 ml of a water/acetonitrile/**acetic** **acid** mixture (1:1:0.1) and filtered. The filtrate was **lyophilized** to yield an unpurified **peptide** as a fluffy powder. This **peptide** was purified by high performance liquid chromatography (HPLC) under the following conditions.

US PAT NO: 5,369,094 [IMAGE AVAILABLE] L1: 5 of 45
DATE ISSUED: Nov. 29, 1994
TITLE: Polypeptide **bombesin** antagonists
INVENTOR: Andrew V. Schally, Metairie, LA
Renzhi Cai, Metairie, LA
ASSIGNEE: The Administrators of the Tulane Educational Fund, New Orleans, LA (U.S. corp.)
APPL-NO: 08/031,325
DATE FILED: Mar. 15, 1993
ART-UNIT: 181
PRIM-EXMR: Lester L. Lee
ASST-EXMR: A. M. Davenport
LEGAL-REP: Omri M. Behr, Matthew J. McDonald

US PAT NO: 5,369,094 [IMAGE AVAILABLE] L1: 5 of 45

ABSTRACT:
Pseudopeptides comprising a peptide of formula I:

X-A.sup.1 -A.sup.2 -Trp-Ala-Val-Gly-His-Leu-.sub.psi -A.sup.9 -Q wherein X is hydrogen, a single bond linking the alpha amino group of A.sup.1 to the gamma carboxyl moiety on the 3-priopionyl moiety of A.sup.2 when A.sup.2 is Glu, or a group of formula R.sup.1 CO-- wherein R.sup.1 is selected from the groups consisting of

a) hydrogen, C.sub.1-10 alkyl, phenyl or phenyl-C.sub.1-10 -alkyl, p-HI-phenyl, p-HI-phenyl-C.sub.1-10 -alkyl, naphthyl, naphthyl-C.sub.1-10 -alkyl, indolyl, indolyl-C.sub.1-10 -alkyl, pyridyl, pyridyl-C.sub.1-10 -alkyl, thienyl, thienyl-C.sub.1-10 -alkyl, cyclohexyl or cyclohexyl-C.sub.1-10 -alkyl, where HI=F, Cl, Br, OH, CH.sub.3 or OCH.sub.3 ;

b) N(R.sup.2)(R.sup.3)--, wherein R.sup.2 is hydrogen, C.sub.1-10 alkyl, phenyl or phenyl-C.sub.1-10 -alkyl, R.sup.3 is hydrogen or C.sub.1-10 alkyl; c) R.sup.4 O--, wherein R.sup.4 is C.sub.1-10 alkyl, phenyl or phenyl-.sub.1-10 -alkyl; A.sup.1 is a D- or L- amino acid residue selected from the group consisting of Phe, p-HI-Phe, pGlu, Nal, Pal, Tpi, unsubstituted Trp or Trp substituted in the benzene ring by one or more members selected from the group consisting of F, Cl, Br, NH.sub.2 or C.sub.1-3 alkyl; or A.sup.1 is a peptide bond linking the acyl

moiety of R.sup.1 CO-- to the alpha amino moiety of A.sup.2 ; A.sup.2 is Gln, Glu[--], Glu(Y) or His, wherein [--] is a single bond linking the gamma carboxyl group of A.sup.2 when A.sup.2 is Glu with the alpha amino group of A.sup.1 where X is a single bond, Y is --OR.sup.5 or --N(R.sup.5)(R.sup.6) wherein R.sup.5 is hydrogen, C.sub.1-3 alkyl or phenyl; R.sup.6 is hydrogen or C.sub.1-3 alkyl; and R.sup.7 is hydrogen, C.sub.1-3 alkyl or --NHCONH.sub.2 ; Leu-y.sub.psi - is a reduced form of Leu wherein the C.dbd.O moiety of Leu is instead --CH.sub.2 -- such that the bond of this --CH.sub.2 -- moiety with the alpha amino moiety of the adjacent A.sup.9 residue is a pseudopeptide bond; A.sup.9 is Tac, MTac, or DMTac; and Q is NH.sub.2 or OQ.sup.1 where Q.sup.1 is hydrogen, C.sub.1-10 alkyl, phenyl or phenyl-C.sub.1-10 -alkyl; and the pharmaceutically acceptable acids or salts thereof.

TITLE: Polypeptide **bombesin** antagonists

SUMMARY:

BSUM(2)

The . . . directed to novel peptides which influence the growth of cancerous tumors in humans. More specifically, the present invention relates to **bombesin** antagonists which are .PSI..sup.8-9 pseudopeptides containing a Tac, MTac, or DMTac residue at the C terminal position, the salts thereof,. . . compositions, methods of synthesizing these peptides and methods of use pertaining to these peptides. These peptides possess antagonist properties against **bombesin** or **bombesin**-like peptides.

SUMMARY:

BSUM(4)

This invention relates to polypeptide compounds which possess antagonist properties against **bombesin** or **bombesin**-like peptides (such as gastrin releasing peptide (GRP), Neuromedin C and the like) hereinafter referred to as **bombesin** antagonist properties and which are of value, for example in the treatment of malignant diseases in warm-blooded organisms such as. . . pharmaceutical compositions containing said polypeptide compounds and processes for the manufacture of medicaments containing them for use in producing a **bombesin** antagonist effect in warm-blooded organisms such as man.

SUMMARY:

BSUM(5)

Bombesin is a tetradecapeptide amide which was first isolated from the skin of the frog Bombina bombina (Anastasi, Erspamer and Bucci, Experientia, 1971, 27, 166). It is known that **bombesin** is a potent mitogen for mouse Swiss 3T3 fibroblast cells (Rozengurt and Sinnett-Smith, Proc. Natl. Acad. Sci. USA, 1983, 80,. . . secretion from guinea pig pancreatic acini (Jensen, Jones, Folkers and Gardner, Nature, 1984, 309, 61). It is also known that **bombesin**-like peptides are produced and secreted by human small-cell lung cancer (SCLC) cells (Moody, Pert, Gazdar, Carney and Minna, Science, 1981, 214, 1246), that exogenously added **bombesin**-like peptides can stimulate the growth of

human SCLC cells in vitro (Carney, Cuttita, Moody and Minna, Cancer Research, 1987, 47, 821) and that a monoclonal antibody specific for the C-Terminus region of **bombesin** and GRP can block binding of GRP to its receptors and prevent the growth of human SCLC cells both in. . .

SUMMARY:

BSUM(6)

GRP which has **bombesin**-like properties is a widely distributed peptide amide containing 27 amino acids isolated from the porcine gut (McDonald, Jornvall, Nilsson, Vagne,. . . Biochem. Biophys. Res. Commun., 1979, 90, 227) in which the C-terminus amino acid sequence is almost identical to that of **bombesin**. Neuromedin C is a decapeptide amide, the structure of which is identical to the last ten amino acids in the. . .

SUMMARY:

BSUM(7)

The structures of **bombesin**, Neuromedin C and Carboxyl-terminal nonapeptide of GRP are shown below: ##STR1##

SUMMARY:

BSUM(8)

The search for other amphibian **bombesin**-like peptides led to the isolation of Litorin, a nonapeptide (pGlu-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH.sub.2)in the skin of frog from Papua, New Guinea which proves to be an extremely potent **bombesin** analogues (Yasukara et al., Chem. Pharm. Bull., 1979, 27, 492). The studies on **bombesin** analogues revealed that a minimum segment of the 9 amino acid residues from position 6 to 14 of **bombesin** possessed the full spectrum of **bombesin** activity.

SUMMARY:

BSUM(9)

Several kinds of **bombesin** antagonists have now been characterized. Substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH.sub.2) Seq. ID No. 26 which has slight amino acid sequence homology with **bombesin** does not inhibit the binding of **bombesin** and **bombesin**-like peptides, but Substance P analogues modified by the replacement of several of L-amino acids with D-amino acids such as (D-Arg.sup.1,. . . D-Phe.sup.5, D-Trp.sup.7,9, Leu.sup.11) Substance P, (Moody et al., Fed. Proceedings, 1987, 46, 2201) were found to block the secreting of **bombesin** in pancreatic acinar cells and to antagonize the growth-promoting effects of **bombesin** in Swiss 3T3 cells. Two types of **bombesin** antagonists derived from **bombesin**, for instance, (D-Phe.sup.6, D-Phe.sup.12) **bombesin**, and [Leu.sup.13 -.sub.psi -Leu.sup.14] **bombesin** (Coy et al., J. Biol. Chem., 1988, 263, 5056 and peptides, 1989, 10, 587) have proved to be potent in vitro and in vivo inhibitors of **bombesin** response.

SUMMARY:

BSUM(10)

Another type of **bombesin** antagonist revealed by Heimbrook et al., (Bio. Chem., 1989, 264, 11258) is N-acetyl-GRP(20-26) and its analogues, wherein the C-terminal methionine residue is deleted from GRP(20-27) analogues. Coy [J. Biol. Chem.. 264, 1989, 25, 14691] reported that some short chain **bombesin** antagonists based on Litorin sequence such as [D-Phe.sup.b 6, Leu.sup.13 -.sub.psi -Phe.sup.14] **bombesin**-(6-14) and [D-Phe.sup.6, Leu.sup.13 -.sub.psi -Leu.sup.14] **bombesin**-(6-14) exhibited much more potency than their corresponding parent peptide [Leu.sup.13 -.sub.psi -Leu.sup.14] **bombesin**.

SUMMARY:

BSUM(11)

Linear (non-cyclic) **bombesin** analogues of GRP and amphibian **bombesin** optionally having a CH.sub.2 --NH non-peptide bond are described in PCT Patent Application WO 90/03980 (and related analogues in WO 91/02746). These analogues, said to act as inhibitors of natural **bombesin** peptides, have the formula ##STR2## where R.sub.1 and R.sub.2 =H; A.degree. may be deleted; among the many possible amino acids. . .

SUMMARY:

BSUM(12)

Linear peptide analogs of **bombesin** are also described in EP 0 309 297. These peptides may have C-terminal Met residue and a [CH.sub.2 --NH] pseudopeptide. . .

SUMMARY:

BSUM(14)

The present invention provides novel polypeptides which are potent **bombesin** antagonists; methods of synthesizing these polypeptides; and medical applications including pharmaceutical compositions comprising said polypeptides and of said polypeptides and. . .

SUMMARY:

BSUM(16)

More particularly, a first embodiment provides potent **bombesin** antagonist pseudopeptides of Formula I: ##STR4## wherein X is hydrogen,

SUMMARY:

BSUM(40)

The **bombesin** antagonists of Formula I may be synthesized by solid phase synthesis. In a first protocol, all the amino acids are. . .

SUMMARY:

BSUM(41)

In . . . solid phase or liquid phase. A tripeptide containing C-terminal is linked with an oligopeptide to form the entire Formula I **bombesin** antagonist.

DRAWING DESC:

DRWD(2)

FIG. 1 is a graph depicting the effect of an MXT mouse mammary cancer of administering certain **bombesin** antagonists, based on data drawn from Table 2, Example 7.

DRAWING DESC:

DRWD(3)

FIG. 2 is a graph depicting the effect on SCLC tumor volume in nude mice of administering certain **bombesin** antagonists, based on data drawn from Table 4, Example 8.

DRAWING DESC:

DRWD(4)

FIG. 3 is a graph depicting the effect on MIA PACA-2 pancreatic tumor volume in nude mice of administering certain **bombesin** antagonists, based on data drawn from Table 5, Example 9.

DRAWING DESC:

DRWD(5)

FIG. 4 is a graph depicting the effect on a CAPAN-2 pancreatic tumor volume in nude mice of administering certain **bombesin** antagonists, based on data drawn from Table 6, Example 10.

DETDESC:

DETD(53)

Peptide . . . however that the convention of numbering amino acid residues in a fragmentary peptide according the corresponding position in the complete **bombesin** antagonist tetradecapeptide is not followed herein unless otherwise noted. If this convention were followed, the residues in the Formula I nonapeptide described herein would be numbered from 6 through 14, and the Trp-Ala-Val-Gly-His-Leu core of the **bombesin** antagonists would be numbered A.sup.8 -A.sup.9 -A.sup.10 -A.sup.11 -A.sup.12 -A.sup.13. To avoid confusion, the **bombesin** antagonists are instead numbered herein as follows: the N-terminal amino acid (or amino acid analogue) residue is A.sup.1 ; the. . .

DETDESC:

DETD(55)

The preferred embodiments are **bombesin** antagonist peptides of Formula I ##STR8## wherein X, A.sup.1, A.sup.2, Leu-.sub.psi, A.sup.9 and Q are defined as above.

DETDESC:

DETD(56)

These **bombesin** antagonist pseudopeptides are characterized by amino acid sequence, particularly at residues A.sup.1, A.sup.2 and A.sup.9 ; as well by the. . .

DETDESC:

DETD(60)

The most particularly preferred pseudopeptide **bombesin** antagonists in the present invention appear below.

DETDESC:

DETD(68)

At least two synthetic protocols may be followed to produce the Formula I pseudopeptide **bombesin** antagonists. In the first protocol, all the amino acids are sequentially linked to one another after the C-terminal residue, A.sup.9. . . on the resin. It is then linked to an oligopeptide carrying the remainder of the amino acid to form the **bombesin** antagonist. In both protocols, synthesis begins at the C-terminal A.sup.9 residue and adds amino acid residues sequentially with growth toward. . .

DETDESC:

DETD(78)

Before describing synthesis of the Formula I **bombesin** antagonists in detail, several synthetic Operations common to one or both of the above protocols are described.

DETDESC:

DETD(87)

d) Synthetic amino acids or amino acid analogs to be incorporated in the **bombesin** antagonist pseudopeptides are generally available from commercial sources. Thus, Hca is commercially available from Aldrich Co., 1001 St. Paul Avenue,. . .

DETDESC:

DETD(120)

In most cases, pseudopeptide **bombesin** antagonists were further purified by rechromatography on the same column with slight modification to the gradient conditions. The homogeneity of. . .

DETDESC:

DETD(137)

The **bombesin** antagonists are useful for the treatment of states of hypergastrinemia, for example, pernicious anemia, chronic atrophic gastritis, Zollinger-Ellison Syndrome, and. . .

DETDESC:

DETD(139)

Since these compounds of this invention are antagonists of **bombesin**/GRP receptors, they can be used in treatment of lung cancer, colon cancer and gastric cancer.

DETDESC:

DETD(140)

The Formula I **bombesin** antagonists of the invention may be administered in the form of pharmaceutically acceptable nontoxic acids or salts, such as acid. . .

DETDESC:

DETD(142)

Treatment . . . may be carried out in the same manner as the clinical treatment using other agonists and antagonists of LHRH, or **somatostatin** analogues. Thus, the Formula I **bombesin** antagonists may be administered intravenously, subcutaneously, intramuscularly, intranasally or by pulmonary aerosol or in a depot form (e.g. microcapsules, microgranules. . .

DETDESC:

DETD(167)

Intermediate . . . phase resulting in a C-terminal Q group which is --NH.sub.2. The peptide is purified with HPLC per Operation 7. The **bombesin** antagonist peptide number 1 is thus obtained.

DETDESC:

DETD(184)

Then, . . . Bom protecting group from His. The solvent is evaporated in vacuo and washed with ethyl acetate, extracted with 70-80% aqueous **acetic** **acid** and **lyophilized**. After purification, **bombesin** antagonist **peptide** number 15 is obtained.

DETDESC:

DETD(191)

These **bombesin** antagonists may suitably be synthesized from a common intermediate I-3, i.e., Fmoc-Gln-Trp-Ala-Val-Gly-His(Bom)-Leu-.sub.psi -Cys(But)-BHA resin. This is built on 1.0 g.. . .

DETDESC:

DETD(214)

Intermediate . . . then extracted with 70-80% acetic acid and lyophilized to yield crude nonapeptide resin. The reaction mixture is purified to yield **bombesin** antagonist peptide number 18.

DETDESC:

DETD(230)

Intermediate . . . removing the Bom protecting group from His. The solvent is evaporated in vacuo and washed with ethylacetate, extracted with 70-80% **acetic** **acid** and **lyophilized**, yielding the following **peptide**: Pal-Gln-Trp-Ala-Val-Gly-His-Leu-.sub.psi -Cys-NH.sub.2.

DETDESC:

DETD(238)

Binding of .sup.125 I-Tyr.sup.4 -**Bombesin** and its displacement by **bombesin** antagonist pseudopeptides is tested in 24-well tissue culture plates (GIBCO) using Swiss 3T3 cells. Murine Swiss 3T3 fibroblasts are maintained. . . nM HEPES-NaOH (pH 7.4), 0.2% BSA and 100 mcg/ml bacitracin). The cells are then incubated with 0.2 nM .sup.125 I-Tyr.sup.4 -**Bombesin** in the presence or absence of different concentrations of antagonists (6.times.10.sup.-11 -6.times.10.sup.-6 M, total volume 0.4 ml).

DETDESC:

DETD(241)

The . . . on Table I below. Varying doses of unlabeled peptide were used to determine the ability to displaced specific .sup.125 I-Tyr.sup.4 -**Bombesin** binding. The mean value of 2-3 independent tests for each peptide (each performed in triplicate) are indicated.

DETDESC:

DETD(242)

TABLE 1

Inhibition of Binding of .sup.125 I--Tyr.sup.4 -**Bombesin** to Swiss 3T3 Cells by **Bombesin** Antagonists	
Peptide No.	K.sub.i [nM]
01	5.0

02 0.078
03 13
04 13
05 0.007
06 4.3
07 0.009
08. . . 0.26
16 12
17 213
18 0.93
19 20
20 13
21 0.07
22 0.074
D--Tpi--Gln--Trp--Ala--Val--Gly--His--Leu- --psi-
0.20
Leu--NH.sub.2
Bombesin.sup.b 0.28

_
.sup.a mean value of 6 tests;
.sup.b mean value of 11 tests.

DETDESC:

DETD(244)

The effect of treatment with **bombesin** antagonists on tumor volume of estrogen independent MXT mouse mammary cancers is tested as follows: 40 female B6D2F.sub.1 mice are. . .

DETDESC:

DETD(250)

These abbreviations for the **bombesin** antagonists employ conventional numbering for a residue of a peptide fragment: each residue is numbered according to the position it bears in the complete fragment. However, the **bombesin** antagonists are more easily compared to other peptides herein if numbered starting with "one" from the N-terminal. Thus, "[D-Tpi.sup.6 -Leu.sup.13. . .

DETDESC:

DETD(251)

The two **bombesin** antagonists are synthesized by solid phase methods. Group 2 of the mice received sustained release formulation of "B1", while group. . .

DETDESC:

DETD(253)

After . . . B., et al. "Growth Inhibition of MXT Mammary Carcinoma by Enhancing Programmed Cell Depth", (apoptosis) with analogues of LH-RH and **somatostatin**). Breast Cancer Res. Treat. 14: 307-314 (1989).

DETDESC:

DETD(254)

The . . . of tumor volume was at 10 days. The differences in tumor volume between the control and those treated with either **bombesin** antagonists as well as between both **bombesin** antagonists are statistically significant. The results of tumor volume measurements appear in Table 2 and are illustrated in FIG. 1.

DETDESC:

DETD(255)

TABLE 2

Effect of **Bombesin** Antagonists on Tumor volume of Estrogen independent MXT mouse mammary Cancers

	Tumor volume at time (days)		
Peptide	10	14. .	.

DETDESC:

DETD(259)

The effect of one **somatostatin** analogue and three **bombesin** antagonists on human small cell lung carcinoma in nude mice is tested as follows: athymic male nude mice approximately 6. . .

DETDESC:

DETD(261)

The first of the drug therapy compounds administered to the nude mice is a **somatostatin** analogue D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH.sub.2, herein designated "S1."

DETDESC:

DETD(262)

The first of the three **bombesin** antagonists is D-Tpi.sup.1 -Gln.sup.2 -Trp.sup.3 -Ala.sup.4 -Val.sup.5 -Gly.sup.6 -His.sup.7 -Leu.sup.8 -.sub.psi -Leu.sup.9 -NH.sub.2, i.e., B1. The second **bombesin** antagonist is [Tpi.sup.6 -Leu.sup.13 -.sub.psi -Tpi.sup.14]Bn(6-14), i.e., D-Tpi.sup.1 -Gln.sup.2 -Trp.sup.3 -Ala.sup.4 -Val.sup.5 -Gly.sup.6 -His.sup.7 -Leu.sup.8 -.sub.psi -Tpi.sup.9 -NH.sub.2 --designated. . .

DETDESC:

DETD(263)

Microgranules . . . 16 mg. These microgranules are injected every 15

days s.c. at the side opposite to the tumor. Each of the **bombesin** antagonists is dissolved in 0.1% dimethyl sulfoxide in saline solution and injected s.c. twice daily at a dose of 20. . .

DETDESC:

DETD(264)

TABLE 4

Effect of **Bombesin** Antagonists on Tumor volume of SCLC Tumors					
Peptide	Tumor volume at time (days)				
0	7	14	21	28	35
Control. . .					

DETDESC:

DETD(266)

The effect on MIA PACA-2 pancreatic cancer tumors by **bombesin** antagonists is measured as follows: Nude mice similar to the ones in Example 8 are injected s.c. with MIA PACA-2. . .

DETDESC:

DETD(267)

The two experimental groups are: a group of mice receiving **bombesin** antagonist peptide 2 and a control group receiving only the injection vehicle solution. 50 ug. of the injection vehicle solution. . .

DETDESC:

DETD(269)

TABLE 5

Effect of **Bombesin** Antagonists on Tumor volume (mm.sup.3) of MIA PACA-2 pancreatic tumors			
Peptide	Tumor volume at time (days)		
0	7	11	15. . .

DETDESC:

DETD(271)

The effect of treatment with as **bombesin** antagonist on nude mice bearing CAPAN-2 human pancreatic cancer is as follows.

DETDESC:

DETD(272)

Nude . . . of mice is divided into two, with the control group

receiving only the injection vehicle solution and the other receiving **bombesin** antagonist Peptide No. 2, 50mg. of which were administered twice daily by s.c. injection.

DETDESC:

DETD(274)

TABLE 6

Effect of **Bombesin** Antagonists on Tumor volume (mm.sup.3) of CAPAN pancreatic tumors

Peptide	Tumor volume at time (days)	
0	7	14. . .

CLAIMS:

CLMS(1)

We claim:

1. A **bombesin** antagonist peptide having the formula:

X-A.sup.1 -A.sup.2 -Trp-Ala-Val-Gly-His-Leu-.sub.psi -A.sup.9 -Q wherein
X is hydrogen,
a single bond linking the. . .

CLAIMS:

CLMS(10)

10. A **bombesin** antagonist peptide having the formula:

X-A.sup.1 -A.sup.2 -Trp-Ala-Val-Gly-His-Leu-.sub.psi -A.sup.9 -Q wherein
X is hydrogen,
a single bond linking the. . .

CLAIMS:

CLMS(11)

11. A **bombesin** antagonist peptide according to claim 1 wherein
X is R.sup.1 CO--,
A.sup.1 is a peptide bond linking the acyl moiety of. . .

US PAT NO: 5,338,668 [IMAGE AVAILABLE] L1: 6 of 45
DATE ISSUED: Aug. 16, 1994
TITLE: Opioid peptides derived from wheat proteins
INVENTOR: Masaaki Yoshikawa, Joyo, Japan
Shin-ichi Fukudome, Kyoto, Japan
ASSIGNEE: Nisshin Flour Milling Co., Ltd., Tokyo, Japan (foreign corp.)
APPL-NO: 08/061,065

DATE FILED: May 14, 1993
ART-UNIT: 188
PRIM-EXMR: Herbert J. Lilling
LEGAL-REP: Oblon, Spivak, McClelland, Maier & Neustadt

US PAT NO: 5,338,668 [IMAGE AVAILABLE] L1: 6 of 45

ABSTRACT:
Disclosed are opioid peptides recovered from hydrolysates of wheat proteins with an acid protease and further a neutral or alkaline protease. Of those peptides, the structure of four opioid peptides was identified by the amino acid sequence of Gly-Tyr-Tyr-Pro (SEQ ID NO: 1), Gly-Tyr-Tyr-Pro-Thr (SEQ ID NO: 2), Gly-Tyr-Tyr-Pro-Thr-Ser (SEQ ID NO: 3) or Tyr-Pro-Ile-Ser-Leu (SEQ ID NO: 4). They are useful as a medicine such as narcotic, analgesic or the like.

DETDESC:

DETD(20)

The . . . in analgesic, narcotic, affection, respiration, pulsation, body temperature, gastrointestinal function, athrocytosis, immunity, regulation of hormone secretion such as insulin and **somatostatin**, enhanced absorption of electrolyte and regulated contraction of myocardium, which may be useful as an analgesic and narcotic agent, a. . .

DETDESC:

DETD(102)

Subsequently, hydrogen fluoride was distilled off under reduced pressure and the residue was extracted with 30% **acetic** **acid** and **lyophilized** to afford 150 mg of a crude **peptide**. The crude **peptide** was purified by reverse-phase chromatography (RPC) using an octadecyl silane (ODS) column (Cosmosil 5 C.sub.18 -AR, Nacalai Tesque Inc.) to. . .

US PAT NO: 5,326,751 [IMAGE AVAILABLE] L1: 7 of 45
DATE ISSUED: Jul. 5, 1994
TITLE: Enkephalin analogs
INVENTOR: Ronald C. Haaseth, Tucson, AZ
Victor J. Hruby, Tucson, AZ
ASSIGNEE: Arizona Board of Regents on behalf of the University of Arizona, Tucson, AZ (U.S. corp.)
APPL-NO: 07/904,425
DATE FILED: Jun. 26, 1992
ART-UNIT: 181
PRIM-EXMR: Merrell C. Cashion, Jr.
ASST-EXMR: S. G. Marshall
LEGAL-REP: Quarles & Brady

US PAT NO: 5,326,751 [IMAGE AVAILABLE] L1: 7 of 45

ABSTRACT:
A new class of opioid receptor analogs is described based on an alanine

substitution in the three position in the enkephalin analog DPDPE. The alanine-substituted analogs show increased selectivity for the delta type of opioid receptors over the mu type of receptors.

DETDESC:

DETD(19)

2.8 . . . ethyl ether. Four extractions with 25 mL portions of glacial acetic acid [HOAc] removed the resin from the mixture. The **peptide**-containing fractions of the **acetic** **acid** extractions were combined and **lyophilized** to a white powder which contained the free disulfhydryl form of the pentapeptide [DPADPE(SH).sub.2].

DETDESC:

DETD(51)

To . . . minor modifications, were set up, except [.sup.3 H]CTOP (30 Ci/mmol, New England Nuclear Inc.), a highly mu-selective peptide analog of **somatostatin**, was used in place of [.sup.3 H][p-Cl-Phe.sup.4]DPDPE.

US PAT NO: 5,268,360 [IMAGE AVAILABLE] L1: 8 of 45
DATE ISSUED: Dec. 7, 1993
TITLE: Opioid peptides derived from wheat proteins
INVENTOR: Masaaki Yoshikawa, Joyo, Japan
Shin-ichi Fukudome, Kyoto, Japan
ASSIGNEE: Nisshin Flour Milling Co., Ltd., Tokyo, Japan (foreign corp.)
APPL-NO: 07/801,388
DATE FILED: Dec. 2, 1991
ART-UNIT: 181
PRIM-EXMR: Merrell C. Cashion, Jr.
ASST-EXMR: Bennett Celsa
LEGAL-REP: Oblon, Spivak, McClelland, Maier & Neustadt

US PAT NO: 5,268,360 [IMAGE AVAILABLE] L1: 8 of 45

ABSTRACT:
Disclosed are opioid peptides recovered from hydrolysates of wheat proteins with an acid protease and further a neutral or alkaline protease. Of those peptides, the structure of four opioid peptides was identified by the amino acid sequence of Gly-Tyr-Tyr-Pro (SEQ ID NO:1), Gly-Tyr-Tyr-Pro-Thr (SEQ ID NO:2), Gly-Tyr-Tyr-Pro-Thr-Ser (SEQ ID NO:3) or Tyr-Pro-Ile-Ser-Leu (SEQ ID NO:4). They are useful as a medicine such as narcotic, analgesic or the like.

DETDESC:

DETD(20)

The . . . in analgesic, narcotic, affection, respiration, pulsation, body temperature, gastrointestinal function, athrocytosis, immunity, regulation of hormone secretion such as insulin and **somatostatin**, enhanced absorption of electrolyte and regulated contraction of

myocardium, which may be useful as an analgesic and narcotic agent, a. . .

DETDESC:

DETD(99)

Subsequently, hydrogen fluoride was distilled off under reduced pressure and the residue was extracted with 30% **acetic** **acid** and **lyophilized** to afford 150 mg of a crude **peptide**. The crude **peptide** was purified by reversed-phase chromatography (RPC) using an octadecyl silane (ODS) column (Cosmosil 5 C.sub.18 -AR, Nacalai Tesque Inc.) to. . .

US PAT NO: 5,262,519 [IMAGE AVAILABLE] L1: 9 of 45
DATE ISSUED: Nov. 16, 1993
TITLE: GRF analogs XI
INVENTOR: Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 07/701,414
DATE FILED: May 15, 1991
ART-UNIT: 181
PRIM-EXMR: Lester L. Lee
ASST-EXMR: A. M. Davenport
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 5,262,519 [IMAGE AVAILABLE] L1: 9 of 45

ABSTRACT:
The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in animals, including humans and also resist enzymatic degradation in the body. Certain preferred peptides have the formula:
(B)R.sub.1 -Ala-Asp-Ala-Ile-Phe-Thr-R.sub.8 -Ser-Tyr-Arg-Lys-Val-Leu-R.sub.15 -R.sub.16 - Leu-Ser-Ala-Arg-Lys-Leu-Leu-R.sub.24 -R.sub.25 -Ile-Nle-R.sub.28 -Arg-Y wherein R.sub.1 is Tyr, D-Tyr, Phe, D-Phe, His or D-His; B is H or N.sup..alpha. Me; R.sub.8 is Ala, Aib or Asn; R.sub.15 is Gly or Ala; R.sub.16 is Ala, Aib or Gln; R.sub.24 is Ala, Aib or Gln; R.sub.25 is Ala, Aib or Asp; R.sub.28 is Ser or Asn; Y is NHR with R being H or lower alkyl; provided that at least one of R.sub.8, R.sub.16, R.sub.24 and R.sub.25 is Ala or Aib.

SUMMARY:

BSUM(3)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, growth hormone releasing factors (GRF) were isolated from extracts of human. . .

DETDESC:

DETD(39)

In . . . of the HF under high vacuum, the resin-peptide remainder is washed alternately with dry diethyl ether and chloroform, and the **peptide** is then extracted with degassed 2N aqueous **acetic** **acid** and separated from the resin by filtration, and **lyophilized**.

US PAT NO: 5,175,146 [IMAGE AVAILABLE] L1: 10 of 45
DATE ISSUED: Dec. 29, 1992
TITLE: Synthetic calcitonin peptides
INVENTOR: Channa Basava, San Diego, CA
Karl Y. Hostetler, Del Mar, CA
ASSIGNEE: Vical, Inc., San Diego, CA (U.S. corp.)
APPL-NO: 07/572,674
DATE FILED: Aug. 24, 1990
ART-UNIT: 181
PRIM-EXMR: Merrell C. Cashion, Jr.
ASST-EXMR: A. M. Davenport
LEGAL-REP: Knobbe, Martens, Olson & Bear

US PAT NO: 5,175,146 [IMAGE AVAILABLE] L1: 10 of 45

ABSTRACT:
Synthetic hypocalcemic peptides which are similar in biological properties to native calcitonins as clinically useful agents. The peptides comprise analogues of native calcitonins having amino acid substitutions and deletions which act to improve potency, prolong duration of the hormonal effect, enhance receptor binding, and increase oral or nasal bioavailability. The calcitonin peptide analogues are less expensive and more easily synthesized than native calcitonins, and have improved resistance to inactivation or degradation. Methods are provided for the synthesis of these peptides.
Also, disclosed are novel cyclic peptides, including calcitonin, having increased stability with respect to proteolysis. Methods for the synthesis of these peptides are provided, comprising converting disulfide cyclic peptides and proteins to enzymatically and chemically stable cyclic peptide structures by the replacement of cysteine residues with dicarboxylic acids and diamino acids. The method is applicable to various naturally occurring peptides, their synthetic analogues or derivatives, and proteins.

SUMMARY:

BSUM(39)

(f) a cyclic analogue of **somatostatin**, having the structure ##STR9##

DETDESC:

DETD(46)

According to another aspect of the invention, therefore, we have synthesized analogues of amylin, calcitonin gene related peptide (CGRP), **somatostatin**, atrial natriuretic peptide, oxytocin and vasopressin wherein the disulfide bridge which forms a cyclic structure has been replaced by a. . . more stable cyclic structure according to the

methods of the invention. The analogues of amylin, calcitonin gene related peptide (CGRP), **somatostatin**, and atrial natriuretic peptide comprise a cyclic structure wherein the cysteine residues that form the disulfide bridge are replaced by. . .

DETDESC:

DETD(52)

Somatostatin peptide analogues can be administered in daily doses of 2 to 20,000 .mu.g/kg subcutaneously for the treatment of acromegaly or. . .

DETDESC:

DETD(68)

The . . . vacuum. The residue was triturated with dry ether (50 ml), filtered and washed with additional quantities of ether (3.times.50 ml). **Peptide** product in the mixture was isolated by extracting with glacial **acetic** **acid** (3.times.50 ml) followed by **lyophilization** to remove the solvent.

DETDESC:

DETD(139)

EXAMPLE 32 ##STR46## The title compound, a novel cyclic analog of **somatostatin**, was prepared starting from Boc-Lys(Fmoc)-O-CH.sub.2 -Resin (2 g, 1 mmol, Omni Biochem, San Diego, CA) and following the procedure described. . .

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US PAT NO: 5,098,995 [IMAGE AVAILABLE] L1: 11 of 45
DATE ISSUED: Mar. 24, 1992
TITLE: GRF Analogs VIIA
INVENTOR: Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
Catherine L. Rivier, La Jolla, CA
ASSIGNEE: The Salk Institute For Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 07/342,751
DATE FILED: Apr. 25, 1989
ART-UNIT: 181
PRIM-EXMR: Lester L. Lee
ASST-EXMR: A. Davenport
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 5,098,995 [IMAGE AVAILABLE] L1: 11 of 45

ABSTRACT:
The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in animals, including humans and also resist enzymatic degradation in the body. The peptides have the sequence: (B)R.sub.1 -R.sub.2 -R.sub.3 -Ala-(Q.sub.1)R.sub.5 -Phe-Thr-R.sub.8 -Ser(Q.sub.2)R.sub.10 -Arg-R.sub.12 -(Q.sub.3)R.sub.13 -Leu-R.sub.15 -Gln-(Q.sub.4)Leu-R.sub.18 -(Q.sub.5)Ala-Arg-R.sub.21 -(Q.sub.6)R.sub.22 -(Q.sub.7)Leu-R.sub.24 -R.sub.25 -(Q.sub.8)R.sub.26 -(Q.sub.9)R.sub.27 -R.sub.28 -Arg-Gln-Gln-Gly-Glu-R.sub.34 -Asn-Gln-Glu-R.sub.38 -R.sub.39 -R.sub.40 -Arg-R.sub.42 -R.sub.43 -R.sub.44 wherein R.sub.1 is Tyr, D-Tyr, Met, Phe, D-Phe, pCl-Phe, Leu, His or D-His; B is H, C.sup.a Me, N.sup.a Me, desamino, Ac or For; R.sub.2 is Ala, D-Ala, NMA or D-NMA; R.sub.3 is Asp or D-Asp; R.sub.5 is Ile or Leu; R.sub.8 is Ser, Asn, Lys, Arg, Asp or Glu; R.sub.10 is Tyr, D-Tyr or Phe; R.sub.12 is Arg or Lys; R.sub.13 is Ile, Val, Leu or Ala; R.sub.15 is Gly or Ala; R.sub.18 is Ser or Tyr; R.sub.21 is Lys, D-Lys, Arg or D-Arg; R.sub.22 is Leu, Ile, Ala or Val; R.sub.24 is Gln or His; R.sub.25 is Asp or Glu; R.sub.26 is Ile or Leu; R.sub.27 is Met, D-Met, Ala, Nle, Ile, Leu, Nva or Val; R.sub.28 is Asn or Ser; R.sub.34 is Ser or Arg; R.sub.38 is Arg or Gln; R.sub.39 is Gly or Arg; R.sub.40 is Ala

or Ser; R.sub.42 is Phe, Ala or Val; R.sub.43 is Asn or Arg; R.sub.44 is a natural amino acid; Q.sub.1 -Q.sub.9 are either H or C.sup.a Me, provided however that one of Q.sub.1 -Q.sub.9 is C.sup.a Me. These peptides may also be used diagnostically, and the C-terminus can be shortened to residue-29.

SUMMARY:

BSUM(3)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, human pancreatic (tumor) releasing factors (hpGRF) were isolated from extracts of. . .

DETDESC:

DETD(115)

The . . . peptide is judged to be substantially pure using TLC and HPLC. The acetate salt is then prepared by dissolving the **peptide** in water and adding IN **acetic** **acid**. The resulting solution is **lyophilized** to yield the acetate salt.

US PAT NO: 5,002,931 [IMAGE AVAILABLE] L1: 12 of 45
DATE ISSUED: Mar. 26, 1991
TITLE: GRF analogs VII
INVENTOR: Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
Catherine L. Rivier, La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 07/053,235
DATE FILED: May 22, 1987
ART-UNIT: 189
PRIM-EXMR: John Doll
ASST-EXMR: Christina Chan
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 5,002,931 [IMAGE AVAILABLE] L1: 12 of 45

ABSTRACT:
The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in animals, including humans, which have resistance to enzymatic degradation in the body, and which have the sequence: (B)R.sub.1 -R.sub.2 -R.sub.3 -Ala-Ile-Phe-Thr-R.sub.8 -Ser-(Q.sub.1)R.sub.10 - Arg-R.sub.12. (Q.sub.2)R.sub.13 -Leu-R.sub.15 -Gln-Leu-Ser-(Q.sub.3)Ala-Arg. R.sub.21 -(Q.sub.4)R.sub.22 -Leu-Gln-Asp-Ile-R.sub.27 -R.sub.28 -Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-R.sub.42 -R.sub.43 -R.sub.44 wherein R.sub.1 is Tyr, D-Tyr, Met, Phe, D-Phe, pCl-Phe, Leu, His or D-His; B is H, C.sup.a Me, N.sup.a Me, desamino, Ac or For; R.sub.2 is Ala, D-Ala, NMA or D-NMA; R.sub.3 is Asp or D-Asp; R.sub.8 is Ser, Asn, Lys, Arg, Asp or Gln; R.sub.10 is Tyr, D-Tyr or Phe; R.sub.12 is Arg or Lys; R.sub.13 is Ile, Val, Leu or Ala; R.sub.15 is Gly or Ala; R.sub.21 is Lys, D-Lys or D-Arg;

R.sub.22 is Leu, Ile, Ala or Val; R.sub.27 is Met, D-Met, Ala, Nle, Ile, Leu, Nva or Val; R.sub.28 is Asn or Ser; R.sub.42 is Phe, Ala or Val; R.sub.43 is Asn or Arg; R.sub.44 is a natural amino acid; Q.sub.1 -Q.sub.4 are either H or C.sup.a Me, provided however that any or all of the residues between R.sub.30 and R.sub.44, inclusive, may be deleted. These peptides as well as their nontoxic salts may also be used diagnostically.

SUMMARY:

BSUM(3)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, human pancreatic (tumor) releasing factors (hpGRF) were isolated from extracts of. . .

DETDESC:

DETD(82)

The . . . peptide is judged to be substantially pure using TLC and HPLC. The acetate salt is then prepared by dissolving the **peptide** in water and adding in **acetic** **acid**. The resulting solution is **lyophilized** to yield the acetate salt.

US PAT NO: 4,914,189 [IMAGE AVAILABLE] L1: 13 of 45
DATE ISSUED: Apr. 3, 1990
TITLE: Synthetic GHRH analogs
INVENTOR: Andrew V. Schally, Metairie, LA
Jozsef Gulyas, Budapest, Hungary
Sandor Bajusz, New Orleans, LA
ASSIGNEE: The Adminstrators of the Tulane Educational Fund, New Orleans, LA (U.S. corp.)
APPL-NO: 07/011,152
DATE FILED: Feb. 5, 1987
ART-UNIT: 186
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Omri M. Behr

US PAT NO: 4,914,189 [IMAGE AVAILABLE] L1: 13 of 45

ABSTRACT:
Human pancreatic GRF (hpGRF), rat hypothalamic GRF (rGRF) and porcine hypothalamic GRF (pGRF) have been earlier characterized and synthesized. The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in animals, including humans, which have resistance to enzymatic degradation in the body, and which have the sequence: ##STR1## wherein Q.sup.1 is an omega or alpha-omega substituted alkyl,
Q.sup.2 is a lower omega-quanidino-alkyl group.
R.sub.2 is Ala, D-Ala, or D-N-Methyl-Ala
R.sub.3 is Asp, D-Asp, Glu, or D-Glu
R.sub.8 is Asn, D-Asn, Ser, or D-Ser
R.sub.10 is Tyr or D-Tyr

R.sub.12 is Lys, D-Lys Arg or Orn
R.sub.13 is Val or Ile
R.sub.14 is Leu or D-Leu
R.sub.15 is Gly, N-Methyl-Gly, or D-Ala
R.sub.17 is Leu or D-Leu
R.sub.18 is Tyr or Ser
R.sub.23 is Leu or D-Leu
R.sub.24 is Gln or His
R.sub.25 is Asp, D-Asp, Glu, or D-Glu
R.sub.27 is Met, D-Met, Ala, Nle, Ile, Val, Nva, Leu
R.sub.28 is Asn or Ser
The peptides as well as nontoxic salts thereof may be administered to animals, including humans and cold-blooded animals, to stimulate the release of GH and may be used diagnostically.

SUMMARY:

BSUM(3)

Physiologists . . . LRF, LH-RH or GnRH) and for the pituitary hormone and adreno-corticotropin (the 41-amino acid polypeptide CRF). An inhibitory factor, called **somatostatin**, has also been characterized in the form of a tetradecapeptide which inhibits the secretion of growth hormone (GH). GH releasing. . .

DETDESC:

DETD(96)

The . . . in vacuo at room temperature. The remaining material was extracted, first with ether (removing the nonpolar side-products), then the crude **peptide** was extracted from the filtered-cake with 10% **acetic** **acid** and the filtrate was **lyophilized**.

US PAT NO: 4,843,064 [IMAGE AVAILABLE] L1: 14 of 45
DATE ISSUED: Jun. 27, 1989
TITLE: GRF analogs V
INVENTOR: Joan Vaughan, San Diego, CA
Joachim Spiess, Encinitas, CA
Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 07/096,513
DATE FILED: Sep. 11, 1987
ART-UNIT: 186
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,843,064 [IMAGE AVAILABLE] L1: 14 of 45

ABSTRACT:
The invention provides peptides which are particularly potent in stimulating the release of pituitary GH in fish and amphibians and which have a substantial portion or all of the following sequence:
His-Ala-Asp-Gly-R.sub.5 -Phe-Asn-Lys-Ala-Tyr-Arg-Lys-Ala-Leu-Gly-Gln-Leu-

Ser-Ala-Arg-Lys-Tyr-Leu-His-Thr-Leu-R.sub.27 -R.sub.28 -R.sub.29 -R.sub.30 -R.sub.31 -Gly-R.sub.33 -R.sub.34 -R.sub.35 -R.sub.36 -R.sub.37 - R.sub.38 -R.sub.39 -R.sub.40 -R.sub.41 -R.sub.42 -R.sub.43 -R.sub.44 -Ser wherein R.sub.5 is Met, Leu, Val, Nva, Gln, Thr, Ile or Nle; R.sub.27 is Met, Leu, Val, Nva, Gln, Thr, Ile or Nle; R.sub.28 is Ala, Ser or Asn; R.sub.29 is Lys or Arg; R.sub.30 is Arg or Gln; R.sub.31 is Val or Gln; R.sub.33 is Gly or Glu; R.sub.34 is Gly, Arg or Ser; R.sub.35 is Ser or Asn; R.sub.36 is Met, Leu, Val, Nva, Gln, Thr, Ile or Nle; R.sub.37 is Ile or Glu; R.sub.38 is Glu, Gln or Arg; R.sub.39 is Asp, Arg or Gly; R.sub.40 is Asp, Ser or Ala; R.sub.41 is Asn, Arg or Lys; R.sub.42 is Glu, Phe, Ala or Val; R.sub.43 is Pro, Asn or Arg; R.sub.44 is Leu or Ala. A sequence beginning at the C-terminus and extending part way or all the way to residue R.sub.27 may be deleted; a 29-residue peptide beginning at the N-terminus may be preferred. These peptides, as well as their nontoxic salts, are considered to be particularly useful in agriculture.

SUMMARY:

BSUM(3)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, human pancreatic (tumor) releasing factors (hpGRF) were isolated from extracts of. . .

DETDESC:

DETD(36)

The . . . peptide is judged to be substantially pure using TLC and HPLC. The acetate salt is then prepared by dissolving the **peptide** in water and adding 1N **acetic** **acid**. The resulting solution is **lyophilized** to yield the acetic acid salt.

DETDESC:

DETD(64)

The . . . peptide is judged to be substantially pure using TLC and HPLC. The acetate salt is then prepared by dissolving the **peptide** in water and adding in **acetic** **acid**. The resulting solution is **lyophilized** to yield the acetic acid salt.

US PAT NO: 4,784,987 [IMAGE AVAILABLE] L1: 15 of 45
DATE ISSUED: Nov. 15, 1988
TITLE: GRF analogs VI
INVENTOR: Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 07/060,149
DATE FILED: Jun. 10, 1987
ART-UNIT: 183
PRIM-EXMR: Delbert R. Phillips

LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,784,987 [IMAGE AVAILABLE] L1: 15 of 45

ABSTRACT:
The invention provides peptides which are potent in stimulating the release of pituitary GH in fish and amphibians which have a substantial portion or all of the following sequence: R.sub.1 -R.sub.2 -R.sub.3 -R.sub.4 -R.sub.5 -Phe-R.sub.7 -R.sub.8 -R.sub.9 -Tyr-Arg-R.sub.12 -R.sub.13 -Leu-R.sub.15 -Gln-Leu-R.sub.18 -Ala-Arg-Lys-R.sub.22 -Leu-R.sub.24 -R.sub.25 -R.sub.26 -R.sub.27 -R.sub.28 -R.sub.29 -R.sub.30 -R.sub.31 -Gly-R.sub.33 -R.sub.34 -R.sub.35 -R.sub.36 -R.sub.37 -R.sub.38 -R.sub.39 -R.sub.40 -R.sub.41 -R.sub.42 -R.sub.43 -R.sub.44 -Ser wherein R.sub.1 is N-Me Tyr, Tyr, desNH.sub.2 -Tyr, D-Tyr, N-Et Tyr, N-Ip Tyr, N-Me His, His, desNH.sub.2 -His, D-His, N-Et His, and N-Ip His; R.sub.2 is Ala, D-Ala or D-NMA; R.sub.3 is Asp or D-Asp; R.sub.4 is Gly or Ala; R.sub.5 and R.sub.27 are selected from the group consisting of Met, Leu, Val, Nva, Gln, Thr, Ile, Ala, Arg, Asn, Asp, Cys, Glu, Gly, His, Nle, Lys, Phe, Pro, Ser, Tyr and Trp; R.sub.7 is Asn or Thr; R.sub.8 is Lys, Asn or Ser; R.sub. 9 is Ala or Ser; R.sub.12 is Lys or Arg; R.sub.13 is Ala, Val or Ile; R.sub.15 is Gly or Ala; R.sub.18 is Ser or Tyr; R.sub.22 is Tyr or Leu; R.sub.24 is His or Gln; R.sub.25 is Thr, Asp, or Glu; R.sub.26 is Leu or Ile; R.sub.28 is Ala, Ser or Asn; R.sub.29 is Lys or Arg; R.sub.30 is Arg or Gln; R.sub.31 is Val or Gln; R.sub.33 is Gly or Glu; R.sub.34 is Gly, Arg or Ser; R.sub.35 is Ser or Asn; R.sub.36 is Met, Leu, Val, Nva, Gln, Thr, Ile or Nle; R.sub.37 is Ile or Glu; R.sub.38 is Glu, Gln or Arg; R.sub.39 is Asp, Arg or Gly; R.sub.40 is Asp, Ser or Ala; R.sub.41 is Asn, Arg or Lys; R.sub.42 is Glu, Phe, Ala or Val; R.sub.43 is Pro, Asn or Arg; R.sub.44 is Leu or Ala; provided however that at least one of the following is present: R.sub.7 is Asn, R.sub.8 is Lys, R.sub.13 is Ala, R.sub.22 is Tyr and R.sub.25 is Thr; and provided further that any or all of the residues after R.sub.27 may be deleted. A 29-residue peptide beginning at the N-terminus may be preferred. These peptides, as well as their nontoxic salts, are considered to be particularly useful in aquiculture.

SUMMARY:

BSUM(4)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, human pancreatic (tumor) releasing factors (hpGRF) were isolated from extracts of. . .

DETDESC:

DETD(29)

The . . . peptide is judged to be substantially pure using TLC and HPLC. The acetate salt is then prepared by dissolving the **peptide** in water and adding 1N **acetic** **acid**. The resulting solution is **lyophilized** to yield the acetic acid salt.

US PAT NO: 4,742,156 [IMAGE AVAILABLE] L1: 16 of 45

DATE ISSUED: May 3, 1988
TITLE: Peptide antagonists of neurokinin B and opthalmic solutions containing them
INVENTOR: David E. Wright, Ambler, PA
ASSIGNEE: McNeilab, Inc., Fort Washington, PA (U.S. corp.)
APPL-NO: 06/902,351
DATE FILED: Aug. 29, 1986
ART-UNIT: 153
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: Nathan M. Nutter
LEGAL-REP: David J. Levy

US PAT NO: 4,742,156 [IMAGE AVAILABLE] L1: 16 of 45

ABSTRACT:
Four decapeptides found to be analgesics and have antagonist activity to Neurokinin B which is also known as Neuromedin K. The decapeptide are of the following formula (I):

A.sup.1 -D-Pro.sup.2 His.sup.3 -D.sup.4 Phe.sup.5 D-Trp.sup.6 Val.sup.7 -D-Trp.sup.8 -Leu.sup.9 -Nle.sup.10 -NH.sub.2 (I)
wherein A.sup.1 and D.sup.4 are Asp or D-Asp amino acids. Also described is an opthalmic solution to treat pain or inflammation and an HPLC separation method using piperidine.

SUMMARY:

BSUM(20)

The . . . compound of interest elutes at the end of the 0 to 0.3M pyridine gradient. The fractions which incude the desired **peptide** were concentrated in vacuo, redissolved in 50% **acetic** **acid** and **lyophilized**. This ion-exchange chromatography step was repeated in the same manner as described above on the desired isolated fraction. Final purification. . .

DETDESC:

DETD(13)

Male, . . . experiments. They were allowed food and water ad libitum and each animal was used only once. Substance P, Neurokinin B, **bombesin** (a compound which induces scratching but is not a tachykinin), [D-Pro.sup.2, D-Trp.sup.7,9]-Substance P.sub.(1-11) and the product of Example 1. . .

DETDESC:

DETD(14)

To determine the activity of substance P, Neurokinin B and **bombesin**, these agonists were injected intrathecally (max. volume 5 ml) according to the method of Hylden et al. described in Eur.. . . the ability and specificity of the Neurokinin B analogs to block the scratching produced by substance P, Neurokinin B and **bombesin**, varying doses of the antagonists were injected simultaneously with that dose of agonist causing 90% of the animals to scratch.. . .

DETDESC:

DETD(15)

TABLE I

Antagonism of Substance P, Neurokinin B and **Bombesin**-Induced Scratching			
Product of	ID.sub.50 vs. NK.sup.a	ID.sub.50 vs SP.sup.a of **Bombesin**.sup.b	% Inhibition
Example 1	0.6 .mu.g (0.3-1.2).sup.c	3.4 .mu.g (2.3-5.2).sup.c	.sup. 30% at 20 .mu.g.sup.b
Example 2			

. . .

DETDESC:

DETD(16)

From . . . Neurokinin B-induced scratching. At doses two times higher than those which blocked tachykinin-induced scratching, there was no significant block of **bombesin**-induced scratching. These data demonstrate that analogs are selective tachykinin antagonists. In particular, it has been demonstrated by G. Holmdahl and. . .

US PAT NO: 4,728,726 [IMAGE AVAILABLE] L1: 17 of 45
DATE ISSUED: Mar. 1, 1988
TITLE: GRF analogs IIIb
INVENTOR: Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/939,342
DATE FILED: Dec. 8, 1986
ART-UNIT: 153
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,728,726 [IMAGE AVAILABLE] L1: 17 of 45

ABSTRACT:
Human GRF(hGRF), rat GRF(rGRF), porcine GRF(pGRF), ovine GRF(oGRF) and bovine GRF(bGRF) have been earlier characterized and synthesized. The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in animals, including humans, which have resistance to enzymatic degradation in the body, and which contain the sequence: R.sub.1 -R.sub.2 -R.sub.3 -Ala-Ile-Phe-Thr-R.sub.8 -Ser-R.sub.10 -Arg-R.sub.12 -R.sub.13 -R.sub.14 -R.sub.15 -Gln-R.sub.17 -R.sub.18 -Ala-Arg-Lys-Leu-R.sub.23 -R.sub.24 -R.sub.25 -Ile-R.sub.27 -R.sub.28 -R.sub.29 -R.sub.30 -R.sub.31 -R.sub.32, wherein R.sub.1 is

Tyr, D-Tyr, Met, Phe, D-Phe, pCl-Phe, Leu, His or D-His having either a C.sup.a Me or N.sup.a Me substitution or being unsubstituted; R.sub.2 is Ala, D-Ala or D-NMA; R.sub.3 is Asp or D-Asp; R.sub.8 is Ser, Asn, D-Ser or D-Asn; R.sub.10 is Tyr or D-Tyr; R.sub.12 is Arg or Lys; R.sub.13 is Ile or Val; R.sub.14 is Leu or D-Leu, R.sub.15 is Gly or D-Ala; R.sub.17 is Leu or D-Leu; R.sub.18 is Tyr or Ser; R.sub.23 is Leu or D-Leu; R.sub.24 is His or Gln; R.sub.25 is Glu, Asp, D-Glu or D-Asp; R.sub.27 is Met, D-Met, Ala, Nle, Ile, Leu, Nva or Val; R.sub.28 is Asn, Ser or desR.sub.28 ; R.sub.29 is Arg, D-Arg or desR.sub.29 ; R.sub.30 is Gln or desR.sub.30 ; R.sub.31 is Glu or desR.sub.31 ; and R.sub.32 is Gly or desR.sub.32. These peptides as well as their nontoxic salts may also be used diagnostically.

SUMMARY:

BSUM(3)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, human pancreatic (tumor) releasing factors (hpGRF) were isolated from extracts of. . .

DETDESC:

DETD(46)

The . . . 990 Peptide Synthesizer on an NEAM resin as in Example IV. Following its removal from the resin and deprotection, the **peptide** is treated with 1 N **acetic** **acid** to produce the acetate salt thereof, prior to **lyophilization**. The **peptide** is judged to be substantially pure using TLC and HPLC.

US PAT NO: 4,684,620 [IMAGE AVAILABLE] L1: 18 of 45
DATE ISSUED: Aug. 4, 1987
TITLE: Cyclic polypeptides having mu-receptor specificity
INVENTOR: Victor J. Hruby, Tucson, AZ
John T. Pelton, Tucson, AZ
ASSIGNEE: Gibson-Stephens Neuropharmaceuticals, Inc., Tucson, AZ (U.S. corp.)
APPL-NO: 06/647,184
DATE FILED: Sep. 4, 1984
ART-UNIT: 153
PRIM-EXMR: Delbert R. Phillips

US PAT NO: 4,684,620 [IMAGE AVAILABLE] L1: 18 of 45

ABSTRACT:
Novel compounds which are capable of binding with enhanced specificity to the mu opioid receptor are disclosed. The compounds are analogs of somatostain and have the formula: ##STR1## wherein X is CONH.sub.2 or CH.sub.2 OH;
Y and Z are independently sulfur or CH.sub.2 ;
R.sup.1 and R.sup.2, which may be the same or different, are hydrogen, methyl, ethyl, cyclopentamethylene, or a lower alkyl group having five or less carbon atoms;

R.sup.3 and R.sup.4, which may be the same or different, are hydrogen, methyl, ethyl, cyclopentamethylene, or a lower alkyl group having five or less carbon atoms, provided, however, that R.sup.1, R.sup.2, R.sup.3, and R.sup.4 may not all be hydrogen;
AA.sub.1 is Phe, D-Phe, phenyl-Gly, D-phenyl-Gly, Tyr, D-Tyr, L-1-Naphthylalanine, D-1-Naphthylalanine, or D-Phe(4-Me);
AA.sub.2 is Tyr, Phe, Tyr(OMe), Phe(4-Me), Tyr(OEt), or Phe(4-Et); and
AA.sub.3 is Lys, Arg, Orn or homo-Arg.
The novel compounds have antagonist activity and may be used to induce pharmacological or therapeutic effects in humans and other animals.

SUMMARY:

BSUM(6)

Somatostatin is a cyclic tetradecapeptide which is known to interact with numerous receptor systems, including the opiate receptors. Natural occurring **somatostatin** has the formula: ##STR2##

SUMMARY:

BSUM(7)

Peptides, such as **somatostatin**, are identified by amino acid sequence using established abbreviations. For example, as used herein, "Ala" stands for Alanine, "Gly" stands. . . acid in the sequence starting with the amino acid at the amino terminus of the peptide chain. For example, the **somatostatin** analog, ##STR3## is written as ##STR4## signifying the 5-12 amino acid residues of naturally occurring **somatostatin**. Additionally, amino acids may exist as stereoisomers in both L and D configurations.

SUMMARY:

BSUM(8)

Somatostatin is believed to exert a variety of hormonal actions such as inhibition of growth hormone release from the pituitary gland,. . .

SUMMARY:

BSUM(10)

The . . . receptor specificity"). The compounds are a series of cyclic, conformationally restricted polypeptides which are analogs of the naturally occurring peptide, **somatostatin**. More specifically, preferred compounds of the present invention are octapeptides and are **somatostatin** analogs of the 5-12 sequence. The novel compounds function as mu antagonists and may be used to induce pharmacological or. . .

SUMMARY:

BSUM(37)

The . . . 3. Table 1 compares the binding properties at the mu opioid

receptor of the compounds of the present invention with **somatostatin**. The increased mu receptor specificity of the compounds of the present invention is shown in Table 1. Specifically, ##STR12## in 7,800 times more potent at the mu opioid receptor than **somatostatin**. ##STR13## has an IC.sub.50 value of 3.5 nM whereas **somatostatin** has an IC50 value of 27,361 nM.

SUMMARY:

BSUM(38)

Additionally, the compounds of the invention were compared with a **somatostatin** 7-10 fragment analog, a **somatostatin** analog (CGP 23,996: having the formula des-Ala.sup.1,Gly.sup.2 -desamino-Cys3-[Tyr.sup.11]-dicarba.sup.3,14 -**somatostatin**) and morphine-HCl.

SUMMARY:

BSUM(39)

Table 2 compares the inhibition of **somatostatin** and the compounds of the present invention to .sup.125 I CGP 23,996 in rat brain membranes. The compounds of the present invention were less potent than **somatostatin**. These tests, therefore, demonstrate that the **somatostatin** analogs of the present invention are extremely mu selective.

DETDESC:

DETD(6)

The . . . the Ehrlich test. A single major peak was obtained (Rf=0.24) which was collected, diluted with 0.2 N acetic acid and **lyophilized**. Final gel filtration on Sephadex G-15 with 5% **acetic** **acid** gave the pure **peptide**, 91 mg (16% yield), as a white, fluffy powder; amino acid analysis: Phe (1.04); Tyr (1:00); Lys (1.06); Thr (1.85);. . .

DETDESC:

DETD(27)

For . . . concentration of test compounds was determined by quantitative amino acid analysis or from published molar extinction coefficients. Specific binding to **somatostatin**, .mu.- and .delta.-opiate receptors was defined as the difference in the amounts of radioligands bound in the absence and presence of 1 .mu.M **somatostatin**, 1 .mu.M naltrexone, or 1 .mu.M Met-enkephalin, respectively. The data were analyzed using nonlinear least squares regression analysis.

DETDESC:

DETD(28)

The . . . agonist. As Table 3 indicates, ##STR23## antagonized the mu agonist, morphiceptin, in the guinea pig ileum test. However, the same

somatostatin analog did not antagonize DPDPE, a delta agonist, in the mouse vas deferens assay. Moreover, the **somatostatin** analog did not antagonize DPDPE even in a 3.3 fold higher concentration.

DETDESC:

DETD(29)

The . . . the electrically induced contractions. The inhibitory effects of morphiceptin alone and morphiceptin in the presence of the presence of 30nM **somatostatin** analog were determined.

DETDESC:

DETD(30)

The . . . electrically induced contractions. Percent inhibition was calculated. The inhibitory effect of DPDPE alone and DPDPE in the presence of the **somatostatin** analog was assessed. The **somatostatin** analog was tested at a concentration of 1,000 nM.

DETDESC:

DETD(32)

TABLE I

THE EFFECT OF **SOMATOSTATIN** AND ITS ANALOGS ON [.sup.3 H]NALOXONE AND [.sup.3 H]DADLE RECEPTOR BINDING TO RAT BRAIN HOMOGENATES

	[.sup.3 H]Naloxone	[.sup.3. . . ##STR31##
2575 0.81		
		3139 0.83
CGP 23,996	>100,000	
		>100,000
##STR32##	61,021	
	1.31	
		38,078
		1.02
SOMATOSTATIN	27,361	
	1.02	
		16,369
		1.09
AcPhe --D-TrpLysThr	51,468	
	1.00	
		5836 0.80

DETDESC:

DETD(33)

TABLE 2

INHIBITION OF .sup.125 I-CGP 23,996

BINDING TO RAT BRAIN HOMOGENATES
BY **SOMATOSTATIN** AND ITS ANALOGS

PEPTIDE	IC.sub.50 (nM)*
SOMATOSTATIN	3.3 .+-. 0.30
CGP 23,996	8.3 .+-. 2.0
##STR33## Thr	170 .+-. 99
##STR34## Thr. . . 780 Thr	400 .+-. 200
AcPhe --D-TrpLysThr	7100 .+-. 870

*Inhibition of .sup.125 Ilabeled CGP 23,996 (des Ala.sup.1, Gly.sup.2desaminoCys.sup.3[Tyr.sup.11]dicarba.sup.3,14 -**somatostatin**.

US PAT NO: 4,665,157 [IMAGE AVAILABLE] L1: 19 of 45
DATE ISSUED: May 12, 1987
TITLE: Peptide antagonists of neurokinin B
INVENTOR: David E. Wright, Ambler, PA
ASSIGNEE: McNeilab, Inc., Fort Washington, PA (U.S. corp.)
APPL-NO: 06/781,839
DATE FILED: Sep. 30, 1985
ART-UNIT: 153
PRIM-EXMR: John Kight
ASST-EXMR: Nathan M. Nutter
LEGAL-REP: David J. Levy

US PAT NO: 4,665,157 [IMAGE AVAILABLE] L1: 19 of 45

ABSTRACT:
Four decapeptides found to be analgesics and have antagonist activity to Neurokinin B which is also known as Neuromedin K. The decapeptides are of the following formula (I):

A.sup.1 -D-Pro.sup.2 -His.sup.3 -D.sup.4 -Phe.sup.5 -D-Trp.sup.6 -Val.sup.7 -D-Trp.sup.8 -Leu.sup.9 -Nle.sup.10 -NH.sub.2 (I)

wherein A.sup.1 and D.sup.4 are Asp or D-Asp amino acids. Also described is an HPLC separation method using piperidine.

SUMMARY:

BSUM(23)

The . . . compound of interest elutes at the end of the 0 to 0.3M pyridine gradient. The fractions which include the desired **peptide** were concentrated in vacuo, redissolved in 50% **acetic** **acid** and **lyophilized**. This ion-exchange chromatography step was repeated in the same manner as described above on the desired isolated fraction. Final purification. . .

DETDESC:

DETD(13)

Male, . . . experiments. They were allowed food and water ad libitum and each animal was used only once. Substance P, Neurokinin B, **bombesin** (a compound which induces scratching but is not a tachykinin), [D-Pro.sup.2,D-Trp.sup.7,9]-Substance P.sub.(1-11) and the product of Example 1 were. . .

DETDESC:

DETD(14)

To determine the activity of substance P, Neurokinin B and **bombesin**, these agonists were injected intrathecally (max. volume 5 ml) according to the method of Hylden et al. described in Eur.. . . the ability and specificity of the Neurokinin B analogs to block the scratching produced by substance P, Neurokinin B and **bombesin**, varying doses of the antagonists were injected simultaneously with that dose of agonist causing 90% of the animals to scratch.. . .

DETDESC:

DETD(15)

TABLE I

Antagonism of Substance P. Neurokinin B and **Bombesin**-Induced Scratching		
Product of	ID.sub.50 vs. NK.sup.a	ID.sub.50 vs SP.sup.a	% Inhibition of **Bombesin**.sup.b
Example 1	0.6(0.3-1.2).sup.c	3.4(2.3-5.2).sup.c	30% at 20 .mu.g.sup.b
Example 2	80% at 10 .mu.g		
. . .			

DETDESC:

DETD(16)

From . . . Neurokinin B-induced scratching. At doses two times higher than those which blocked tachykinin-induced scratching, there was no significant block of **bombesin**-induced scratching. These data demonstrate that analogs are selective tachykinin antagonists.

US PAT NO: 4,610,976 [IMAGE AVAILABLE] L1: 20 of 45
DATE ISSUED: Sep. 9, 1986
TITLE: Porcine GRF
INVENTOR: Peter Bohlen, Encinitas, CA
Frederick S. Esch, Oceanside, CA
Nicholas C. Ling, San Diego, CA
Paul E. Brazeau, Jr., San Diego, CA

Roger C. L. Guillemin, La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/527,292
DATE FILED: Aug. 29, 1983
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: F. T. Moezie
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,610,976 [IMAGE AVAILABLE] L1: 20 of 45

ABSTRACT:
The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in mammals and which have the formula: H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala-Arg-Val-Arg-Leu-Y wherein Y is OH or NH.sub.2. These peptides or biologically active fragments thereof, or analogs thereof having well-known substitutions and, or additions, as well as nontoxic salts of any of the foregoing, may be administered therapeutically to mammals, including humans, and may be used diagnostically. The peptides are useful in stimulating the release of GH and accelerating growth in warm-blooded non-human animals, particularly pigs, and in improving aquiculture.

SUMMARY:

BSUM(4)

An inhibitory factor was earlier characterized in the form of hypothalamic **somatostatin** which inhibits, at the pituitary level, the secretion of growth hormone. In 1982, a corresponding hypothalamic releasing factor for pituitary. . .

DETDESC:

DETD(6)

After . . . of the HF under high vacuum, the resin-peptide remainder is washed alternately with dry diethyl ether and chloroform, and the **peptide** is then extracted with degassed 2 N aqueous **acetic** **acid**. **Lyophilization** of the **acetic** **acid** extract provides a white fluffy material.

US PAT NO: 4,605,643 [IMAGE AVAILABLE] L1: 21 of 45
DATE ISSUED: Aug. 12, 1986
TITLE: Ovine GRF
INVENTOR: Peter Bohlen, Encinitas, CA
Paul E. Brazeau, Outremont, Canada
Frederick S. Esch, Oceanside, CA
Nicholas C. Ling, San Diego, CA
William B. Wehrenberg, San Diego, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/585,814

DATE FILED: Mar. 2, 1984
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: F. T. Moezie
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,605,643 [IMAGE AVAILABLE] L1: 21 of 45

ABSTRACT:
A synthetic peptide is extremely potent in stimulating the release of pituitary GH in mammals, particularly in sheep, since it is the replicate of the native (hormone) releasing factor of the sheep hypothalamus. It contains the following sequence: Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Ile-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Asn-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala-Lys-Val-Arg-Leu. This peptide or a biologically active fragment thereof, or analogs thereof having well-known substitutions and/or additions, as well as nontoxic salts of any of the foregoing, may be administered therapeutically to mammals and may be used diagnostically. The peptide is particularly useful in stimulating the release of GH so as to accelerate growth in warm-blooded non-human animals, particularly sheep, and/or to improve aquiculture.

SUMMARY:

BSUM(4)

An inhibitory factor was earlier characterized in the form of hypothalamic **somatostatin** which inhibits, at the pituitary level, the secretion of growth hormone. In 1982, a corresponding hypothalamic releasing factor for pituitary. . .

DETDESC:

DETD(8)

After . . . of the HF under high vacuum, the resin-peptide remainder is washed alternately with dry diethyl ether and chloroform, and the **peptide** is then extracted with degassed 2N aqueous **acetic** **acid**. **Lyophilization** of the **acetic** **acid** extract provides a white fluffy material.

US PAT NO: 4,585,756 [IMAGE AVAILABLE] L1: 22 of 45
DATE ISSUED: Apr. 29, 1986
TITLE: Bovine GRF
INVENTOR: Paul E. Brazeau, Jr., San Diego, CA
Peter Bohlen, Encinitas, CA
Frederick S. Esch, Oceanside, CA
Nicholas C. Ling, San Diego, CA
Roger C. L. Guillemin, La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/541,167
DATE FILED: Oct. 12, 1983
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips

ASST-EXMR: F. T. Moezie
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,585,756 [IMAGE AVAILABLE] L1: 22 of 45

ABSTRACT:
The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in mammals and which have the formula: H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Asn-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala-Lys-Val-Arg-Leu-Y wherein Y is OH or NH.sub.2. These peptides or biologically active fragments thereof, or analogs thereof having well-known substitutions and/or additions, as well as nontoxic salts of any of the foregoing, may be administered therapeutically to mammals, including humans, and may be used diagnostically. The peptides are useful in stimulating the release of GH so as to accelerate growth in warm-blooded non-human animals, particularly cattle, and/or to increase the production of milk in lactating cows, and also in improving aquiculture.

SUMMARY:

BSUM(4)

An inhibitory factor was earlier characterized in the form of hypothalamic **somatostatin** which inhibits, at the pituitary level, the secretion of growth hormone. In 1982, a corresponding hypothalamic releasing factor for pituitary. . .

DETDESC:

DETD(6)

After . . . of the HF under high vacuum, the resin-peptide remainder is washed alternately with dry diethyl ether and chloroform, and the **peptide** is then extracted with degassed 2N aqueous **acetic** **acid**. **Lyophilization** of the **acetic** **acid** extract provides a white fluffy material.

US PAT NO: 4,547,489 [IMAGE AVAILABLE] L1: 23 of 45
DATE ISSUED: Oct. 15, 1985
TITLE: Conformationally restricted thymopentin-like compounds
INVENTOR: Gideon Goldstein, Short Hills, NJ
George Heavner, Flemington, NJ
Tapan Audhya, Bridgewater, NJ
Foe-Siong Tjoeng, Neshanic Station, NJ
ASSIGNEE: Ortho Pharmaceutical Corporation, Raritan, NJ (U.S. corp.)
APPL-NO: 06/618,968
DATE FILED: Jun. 11, 1984
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Geoffrey G. Dellenbaugh

US PAT NO: 4,547,489 [IMAGE AVAILABLE] L1: 23 of 45

ABSTRACT:

Immunoregulating peptides are disclosed which are cyclic peptides similar to thymopentin. These peptides are useful for their effects on the immune system, especially the treatment of thymic deficiencies.

DETDESC:

DETD(68)

Cyclo-[Arg-Lys-Asp-Val-Tyr-Gly] . . . (20 ml; 9:1) at 0.degree. C. for 1 h. The peptide resin mixture was washed with diethylether (3.times.20 ml). The **peptide** was extracted with 5 aqueous **acetic** **acid** (3.times.20 ml) and **lyophilized**. The crude material was chromatographed on a Sephadex SPC-25 column (60 cm.times.2.5 cm), equilibrated with 0.2M NH OAc, pH 5.25. . .

DETDESC:

DETD(136)

For comparison, other peptides such as insulin, glucagon, growth hormone, **somatostatin**, .beta.-endorphin, FTS, ACTH, CRF, and ubiquitin caused no detectable displacement.

US PAT NO: 4,528,190 [IMAGE AVAILABLE] L1: 24 of 45
DATE ISSUED: Jul. 9, 1985
TITLE: GRF Analogs IV
INVENTOR: Wylie W. Vale, Jr., La Jolla, CA
Jean E. F. Rivier, La Jolla, CA
ASSIGNEE: The Salk Institute For Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/611,844
DATE FILED: May 18, 1984
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: F. T. Moezie
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,528,190 [IMAGE AVAILABLE] L1: 24 of 45

ABSTRACT:
Human GRF(hGRF), rat GRF(rGRF) porcine GRF(pGRF) and bovine GRF(bGRF) have been earlier characterized and synthesized. The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in animals, including humans, which have resistance to enzymatic degradation in the body, and which have the sequence: R.sub.1 -R.sub.2 -R.sub.3 -Ala-Ile-Phe-Thr-R.sub.8 -Ser-R.sub.10 -Arg-R.sub.12 -R.sub.13 -R.sub.14 -R.sub.15 -Gln-R.sub.17 -R.sub.18 -Ala-Arg-Lys-Leu-R.sub.23 -R.sub.24 -R.sub.25 -Ile-R.sub.27 -R.sub.28 -R.sub.29 -Gln-Gln-Gly-Glu-R.sub.34 -Asn-Gln-Glu-R.sub.38 -R.sub.39 -R.sub.40 -Arg-R.sub.42 -R.sub.43 -R.sub.44 wherein R.sub.1 is Tyr, D-Tyr, Met, Phe, D-Phe, pCl-Phe, Leu, His or D-His having either a C.sup..alpha. Me or N.sup..alpha. Me substitution or being unsubstituted; R.sub.2 is Ala, D-Ala or D-NMA; R.sub.3 is Asp or D-Asp; R.sub.8 is Ser, Asn, D-Ser or D-Asn; R.sub.10 is Tyr or D-Tyr; R.sub.12 is Arg or Lys; R.sub.13 is Ile or Val; R.sub.14 is Leu or D-Leu; R.sub.15 is Gly or D-Ala; R.sub.17 is Leu or D-Leu; R.sub.18 is Tyr or Ser; R.sub.23 is Leu

or D-Leu; R.sub.24 is His or Gln; R.sub.25 is Glu, Asp, D-Glu or D-Asp; R.sub.27 is Met, D-Met, Ala, Nle, Ile, Leu, Nva or Val; R.sub.28 is Asn or Ser; R.sub.29 is Arg or D-Arg; R.sub.34 is Arg or Ser; R.sub.38 is Gln or Arg; R.sub.39 is Arg or Gly; R.sub.40 is Ser or Ala; R.sub.42 is Phe, Ala or Val; R.sub.43 is Asn or Arg; R.sub.44 is a natural amino acid; provided however that any or all of the residues between R.sub.28 and R.sub.44, inclusive, may be deleted and provided also that R.sub.2 is D-NMA and/or R.sub.14 is D-Leu and/or R.sub.29 is D-Arg. These peptides as well as their nontoxic salts may also be used diagnostically.

SUMMARY:

BSUM(3)

Physiologists . . . or inhibit the secretion of each pituitary hormone. A hypothalamic inhibitory factor was characterized in 1972 in the form of **somatostatin** which inhibits the secretion of growth hormone(GH). In 1982, human pancreatic (tumor) releasing factors (hpGRF) were isolated from extracts of. . .

DETDESC:

DETD(113)

The . . . peptide is judged to be substantially pure using TLC and HPLC. The acetate salt is then prepared by dissolving the **peptide** in water and adding 1N **acetic** **acid**. The resulting solution is **lyophilized** to yield the acetic acid salt.

US PAT NO: 4,517,181 [IMAGE AVAILABLE] L1: 25 of 45
DATE ISSUED: May 14, 1985
TITLE: Mammalian PGRF
INVENTOR: Nicholas C. Ling, San Diego, CA
Frederick S. Esch, Oceanside, CA
Peter Bohlen, Encinitas, CA
Paul E. Brazeau, Jr., San Diego, CA
Roger C. L. Guillemin, La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/418,248
DATE FILED: Sep. 15, 1982
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: F. T. Moezie
LEGAL-REP: Fitch, Even, Tabin & Flannery

US PAT NO: 4,517,181 [IMAGE AVAILABLE] L1: 25 of 45

ABSTRACT:
PGRF has been synthesized. The invention provides synthetic peptides which are extremely potent in stimulating the release of pituitary GH in mammals and which have the formula: ##STR1## wherein R is OH or NH.sub.2, R.sub.34 is Ser or Ala, R.sub.38 is Arg or Ser, R.sub.40 is Ala or Arg and R.sub.41 is Arg, Arg-Ala, Arg-Ala-Arg, Arg-Ala-Arg-Leu or des-R.sub.41. These peptides or biologically active fragments thereof, or analogs thereof having well-known substitutions and/or additions, as well

as nontoxic salts of any of the foregoing, may be administered therapeutically to mammals, including humans, and may be used diagnostically.

SUMMARY:

BSUM(4)

Since . . . the pituitary hormones .beta.-endorphin and adrenocorticotropin (the 41-amino acid polypeptide CRF). In addition, an inhibitory factor has been characterized: hypothalamic **somatostatin** inhibits, at the pituitary level, the secretion of growth hormone. Each of these hypothalamic releasing factors and **somatostatin** have been reproduced by total synthesis, and many analogs of the native structures have been synthesized, some with far greater. . .

SUMMARY:

BSUM(6)

Another major problem in the isolation of hypothalamic GRF has been the presence in hypothalamic extracts of very large amounts of **somatostatin** which of course prevent or would give aberrant results in any attempted bioassay. Over the last few years, several laboratories. . .

DETDESC:

DETD(6)

After . . . of the HF under high vacuum, the resin-peptide remainder is washed alternately with dry diethyl ether and chloroform, and the **peptide** is then extracted with degassed 2N aqueous **acetic** **acid**. **Lyophilization** of the **acetic** **acid** extract provides a white fluffy material.

US PAT NO: 4,505,853 [IMAGE AVAILABLE] L1: 26 of 45
DATE ISSUED: Mar. 19, 1985
TITLE: Enzyme-resistant immunomodulatory peptides
INVENTOR: Gideon Goldstein, Short Hills, NJ
George Heavner, Flemington, NJ
Daniel Kroon, Bridgewater, NJ
Tapan Audhya, Bridgewater, NJ
ASSIGNEE: Ortho Pharmaceutical Corporation, Raritan, NJ (U.S. corp.)
APPL-NO: 06/553,281
DATE FILED: Nov. 18, 1983
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Geoffrey G. Dellenbaugh

US PAT NO: 4,505,853 [IMAGE AVAILABLE] L1: 26 of 45

ABSTRACT:
Peptides which have thymopoeitin-like or splenin-like activity combined with greatly increased resistance to degradation by enzymes. The peptides are useful for treatment of immunoregulatory disorders. Also provided are

methods of treating immunoregulatory disorders and compositions used in these methods.

DETDESC:

DETD(4)

The . . . 75 minutes. The HF was removed under reduced pressure. The residue was washed with ethyl acetate and ether, then the **peptide** extracted from the resin with 100 ml 5 percent **acetic** **acid**. The **lyophilized** extract weighed 1.042 g.

DETDESC:

DETD(69)

The . . . hour. The HF was removed with vacuum. The peptide was precipitated with ethyl acetate-ether and washed with this solvent. The **peptide** was dissolved in 3 percent **acetic** **acid** and **lyophilized**. The product weighed 276 mg.

DETDESC:

DETD(77)

The . . . m-cresol at 0 for 50 minutes. After evaporating the HF, the product was washed with ethyl acetate and ether. The **peptide** was extracted with 100 ml 5 percent **acetic** **acid**. The filtered solution was **lyophilized** yielding 798 mg crude product.

DETDESC:

DETD(84)

The . . . for one hour. The HF was removed with vacuum and the residue was washed with ethyl acetate and ether. The **peptide** was extracted with 150 ml 2 percent **acetic** **acid**. The filtered extract was **lyophilized**, yielding 688 mg product.

DETDESC:

DETD(222)

The . . . 0.degree. for one hour. After vacuum removal of the HF, the residue was washed with ethyl acetate and ether. The **peptide** was extracted with 100 ml 5 percent aqueous **acetic** **acid**. The extract was **lyophilized**, yielding 658 mg crude **peptide**.

DETDESC:

DETD(348)

For comparison, other peptides such as insulin, glucagon, growth hormone, **somatostatin**, .beta.-endorphin, FTS, ACTH, CRF, and ubiquitin caused no detectable displacement.

US PAT NO: 4,423,037 [IMAGE AVAILABLE] L1: 27 of 45
DATE ISSUED: Dec. 27, 1983
TITLE: Inhibitors of peptide hormone action
INVENTOR: Michael Rosenblatt, Newton Highlands, MA
John T. Potts, Jr., West Newton, MA
ASSIGNEE: The General Hospital Corporation, Boston, MA (U.S. corp.)
APPL-NO: 06/377,839
DATE FILED: May 13, 1982
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Oblon, Fisher, Spivak, McClelland & Maier

US PAT NO: 4,423,037 [IMAGE AVAILABLE] L1: 27 of 45

ABSTRACT:
The present invention relates to the use of peptide hormone analogues as inhibitors of their respective naturally occurring peptide hormone. The structure of the peptide hormone analogues is exemplified by parathyroid hormone wherein the three N-terminal amino acids are removed and zero or more of the next four N-terminal amino acids are removed sequentially from the N-terminus.

DETDESC:

DETD(12)

Other . . . growth hormone releasing hormone; thyrotropin releasing hormone; prolactin releasing hormone; melanocyte stimulating hormone releasing hormone; growth hormone release inhibiting hormone; **somatostatin**, prolactin release inhibiting hormone, melanocyte stimulating hormone release inhibiting hormone, gonadocrinin, gonadostatin, and somatomedin.

DETDESC:

DETD(33)

The . . . by distillation under reduced pressure (oil vacuum pump). The peptide-resin mixture was washed with anhydrous ether to remove anisole. The **peptide** was then extracted by alternate washes of glacial **acetic** **acid** and water (4x each). The washes were combined and **lyophilized** to yield the crude **peptide**.

DETDESC:

DETD(34)

Crude . . . was purified initially by gel filtration on a Bio-Gel P-6 (Bio-Rad Laboratories) column (5.0.times.100 cm) and eluted with 1 M **acetic** **acid**. After **lyophilization**, the partially purified **peptide** was applied to a carboxymethylcellulose (CM-52, Whatman) ion-exchange column (1.2.times.15 cm). An LKB Ultragrad apparatus created a shallow-sloped conductivity gradient. . .

US PAT NO: 4,411,890 [IMAGE AVAILABLE] L1: 28 of 45
DATE ISSUED: Oct. 25, 1983

TITLE: Synthetic peptides having pituitary growth hormone releasing activity

INVENTOR: Frank A. Momany, Memphis, TN
ASSIGNEE: Beckman Instruments, Inc., Fullerton, CA (U.S. corp.)

APPL-NO: 06/335,011
DATE FILED: Dec. 28, 1981
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: R. J. Steinmeyer, J. E. Vanderburgh, R. S. Frieman

US PAT NO: 4,411,890 [IMAGE AVAILABLE] L1: 28 of 45

ABSTRACT:
Novel peptides having the following amino acid sequence ##STR1## wherein X.sub.1, X.sub.2, and X.sub.3 are selected from a group consisting of N-terminal and desamino alpha-carbon substitutions and a and b are 0 or 1, provided that a and b are always 0 when A.sub.1 is a desamino residue; A.sub.1 and A.sub.4 are selected from a group consisting of histidyl, arginyl, lysyl, .alpha.-naphthylalanyl, .beta.-naphthylalanyl, isoquinolyl, tyrosyl, tryptophyl, phenylalanyl, homologues and analogues thereof, and, with respect to A.sub.1 only the desamino forms thereof; A.sub.2 and A.sub.5 are selected from a group consisting of D-histidyl, D-arginyl, D-lysyl, D-.alpha.-naphthylalanyl, D-.beta.-naphthylalanyl, D-isoquinolyl, D-tyrosyl, D-tryptophyl, D-phenylalanyl, homologues and analogues thereof; A.sub.3 is selected from a group consisting of glycyl, alanyl, valyl, leucyl, isoleucyl, prolyl, seryl, threonyl, methionyl, aspartyl, glutamyl, asparginyl, glutaminyl, histidyl, D-alanyl, D-valyl, D-leucyl, D-isoleucyl, D-prolyl, D-seryl, D-threonyl, D-methionyl, D-aspartyl, D-glutamyl, D-asparaginyl, D-glutaminyl, D-histidyl, and homologues and analogues thereof; A.sub.6 is selected from a group consisting of amino acids of the L- and D- configuration, homologues and analogues thereof, and the descarboxy forms thereof; and Y is selected from a group consisting of C-terminal and descarboxy alpha-carbon substitutions; and the pharmaceutically acceptable salts thereof.

SUMMARY:

BSUM(10)

Various . . . growth hormone to be released from the pituitary by acting in some fashion on the hypothalmus perhaps either to decrease **somatostatin** secretion or to increase an unknown endogenous growth hormone-releasing hormone or both.

SUMMARY:

BSUM(54)

The . . . in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that **somatostatin** inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth. . . other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., **bombesin**; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The peptides of Formula I can also be employed to investigate the. . .

DETDESC:

DETD(29)

The **peptide** was removed from the resin by extraction with 30% aqueous **acetic** **acid** (aq.HOAc). The aq.HOAc was **lyophilized** off to yield a fluffy **peptide** powder.

DETDESC:

DETD(102)

The **peptide** was removed from the resin by extraction with aqueous **acetic** **acid** (aq.HOAc). The aq.HOAc was **lyophilized** off to yield a fluffy **peptide** powder.

DETDESC:

DETD(335)

By introducing various other hormones, e.g., **somatostatin**, testosterone, cortisol, insulin, etc., into the incubation medium of Examples 11-20, one can study what effect these latter hormones have.

US PAT NO: 4,410,513 [IMAGE AVAILABLE] L1: 29 of 45
DATE ISSUED: Oct. 18, 1983
TITLE: Synthetic peptides having pituitary growth hormone releasing activity
INVENTOR: Frank A. Momany, Memphis, TN
ASSIGNEE: Beckman Instruments, Inc., Fullerton, CA (U.S. corp.)
APPL-NO: 06/335,000
DATE FILED: Dec. 28, 1981
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: F. T. Moezie
LEGAL-REP: R. J. Steinmeyer, J. E. Vanderburgh, Robert S. Frieman

US PAT NO: 4,410,513 [IMAGE AVAILABLE] L1: 29 of 45

ABSTRACT:
Pentapeptides which act directly on the pituitary to release growth hormone therefrom.

SUMMARY:

BSUM(10)

Various . . . growth hormone to be released from the pituitary by acting in some fashion on the hypothalmus perhaps either to decrease **somatostatin** secretion or to increase an unknown endogenous growth hormone-releasing hormone or both.

SUMMARY:

BSUM(71)

The . . . in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that **somatostatin** inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth. . . other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., **bombesin**; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The peptides of Formula I can also be employed to investigate the. . .

DETDESC:

DETD(32)

The **peptide** was removed from the resin by extraction with aqueous **acetic** **acid** (aq.HOAc). The aq.HOAc was **lyophilized** off to yield a fluffy **peptide** powder.

DETDESC:

DETD(158)

By introducing various other hormones, e.g., **somatostatin**, testosterone, cortisol, insulin, etc., into the incubation medium of Examples 11-20, one can study what effect these latter hormones have. . .

US PAT NO: 4,410,512 [IMAGE AVAILABLE] L1: 30 of 45
DATE ISSUED: Oct. 18, 1983
TITLE: Combinations having synergistic pituitary growth hormone releasing activity
INVENTOR: Cyril Y. Bowers, New Orleans, LA
ASSIGNEE: Beckman Instruments, Inc., Fullerton, CA (U.S. corp.)
APPL-NO: 06/334,488
DATE FILED: Dec. 28, 1981
ART-UNIT: 123
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: F. T. Moezie
LEGAL-REP: Robert J. Steinmeyer, John E. Vanderburgh, Robert S. Frieman

US PAT NO: 4,410,512 [IMAGE AVAILABLE] L1: 30 of 45

ABSTRACT:
Novel combinations comprising (a) at least one peptide having the following amino acid sequence ##STR1## wherein X.sub.1, X.sub.2, and X.sub.3 are selected from a group consisting of N-terminal and desamino alpha-carbon substitutions and a and b are 0 or 1, provided that a and b are always 0 when A.sub.1 is a desamino residue; A.sub.1 and A.sub.4 are selected from a group consisting of histidyl, arginyl, lysyl, .alpha.-naphthylalanyl, .beta.-naphthylalanyl, isoquinolyl, tyrosyl, tryptophyl, phenylalanyl, homologues and anlogues thereof, and, with respect to A.sub.1 only the desamino forms thereof; A.sub.2 and A.sub.5 are selected from a group consisting of D-histidyl, D-arginyl, D-lysyl,

D-.alpha.-naphthylalanyl, D-.beta.-naphthylalanyl, D-isoquinolyl, D-tyrosyl, D-tryptophyl, D-phenyalanyl, homologues and analogues thereof; A.sub.3 is selected from a group consisting of glycyl, alanyl, valyl, leucyl, isoleucyl, prolyl, seryl, threonyl, methionyl, aspartyl, glutamyl, asparginyl, glutaminyl, histidyl, D-alanyl, D-valyl, D-leucyl, D-isoleucyl, D-prolyl, D-seryl, D-threonyl, D-methionyl, D-aspartyl, D-glutamyl, D-asparaginyl, D-glutaminyl, D-histidyl, and homologues and analogues thereof; A.sub.6 is selected from a group consisting of amino acids of the L- and D- configuration, homologues and analogues thereof, and the decarboxy forms thereof; and Y is selected from a group consisting of C-terminal and descarboxy alpha-carbon substitutions; and the pharmaceutically acceptable salts thereof; and (b) a growth promoting agent.

SUMMARY:

BSUM(10)

Various . . . growth hormone to be released from the pituitary by acting in some fashion on the hypothalmus perhaps either to decrease **somatostatin** secretion or to increase an unknown endogenous growth hormone-releasing hormone or both.

SUMMARY:

BSUM(42)

The . . . in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that **somatostatin** inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth. . . other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., **bombesin**; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The combinations of this invention can also be employed to investigate the. . .

DETDESC:

DETD(34)

The **peptide** was removed from the resin by extraction with aqueous **acetic** **acid** (aq.HOAc). The aq.HOAc was **lyophilized** off to yield a fluffy **peptide** powder.

DETDESC:

DETD(50)

By introducing various other hormones, e.g., **somatostatin**, testosterone, cortisol, insulin, etc., into the incubation medium of Example 3, one can study what effect these latter hormones have. . .

US PAT NO: 4,331,661 [IMAGE AVAILABLE] L1: 31 of 45
DATE ISSUED: May 25, 1982
TITLE: **Bombesin** analogs

INVENTOR: Walter E. Marki, Zurich, Switzerland
Marvin R. Brown, La Jolla, CA
Jean E. F. Rivier, La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 06/193,621
DATE FILED: Oct. 3, 1980
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Fitch, Even, Tabin, Flannery & Welsh

US PAT NO: 4,331,661 [IMAGE AVAILABLE] L1: 31 of 45

ABSTRACT:
Peptides having thermoregulative and analgesic properties when administered to animals. The peptides are identified by the structure:

R.sub.1 -R.sub.2 -Trp-Ala-Val-R.sub.3 -His-Leu-Met-NH.sub.2
wherein: R.sub.1 is an acyl moiety selected from the group consisting of formyl, acetyl, propionyl, acrylyl and benzoyl; R.sub.2 is selected from the group consisting of Gly and the D- and L-isomers of Ala, Asn, Gln, His, Leu, Met, Phe, Ser, Thr and Val; R.sub.3 is selected from the group consisting of D-Ala and Gly. Intermediates of the peptides are also provided.
TITLE: **Bombesin** analogs

SUMMARY:

BSUM(8)

U.S. Pat. No. 4,207,311, issued June 10, 1980 to Marvin R. Brown, et al. discloses the structure of **bombesin** and other related peptides which have been isolated from the skin of several anuran species. Amphibian **bombesin** has the formula:

SUMMARY:

BSUM(10)
The patent discloses that the administration of **bombesin** to mammals, including humans, can be used for reducing the body temperature of the mammal as well as for inducing analgesia. The patent also discloses several analogs of **bombesin** which exhibit certain analgesic and thermoregulative effects in mammals including the octapeptide D-pGlu-Trp-Ala-Val-D-Ala-His-Leu-Met-NH.sub.2. Although this octapeptide is more potent than neurotensin, it is less potent than **bombesin**, and more potent analogs having these properties would be of great value.

SUMMARY:

BSUM(12)

Octapeptides . . . synthesized which are very substantially more potent than neurotensin and which have potencies substantially equal to or significantly greater than **bombesin**. These octapeptides are generally characterized by their resemblance to the eight-member fragment of **bombesin** at the C-terminal end thereof, sometimes referred to as amphibian **bombesin** residues 7-14, or BN.sub.a (7-14). More

specifically, the amino acid residue at the N-terminal has its .alpha.-amino group acylated with. . .

SUMMARY:

BSUM(14)

The . . . Ser, Thr or Val. The remaining seven members of the chain are substantially the same as the C-terminal end of **bombesin**; however, D-Ala can be substituted for Gly.

DETDESC:

DETD(12)

The . . . to HF treatment. After the removal of HF under vacuum, the resin is washed with ethyl ether, extracted with 50% **acetic** **acid**, and **lyophilized** to provide a crude **peptide** powder.

DETDESC:

DETD(23)

TABLE II

PEPTIDE	DOSAGE	CORE TEMPERATURE .degree.C.
Control	--	36.5.degree.
Neurotensin	100 .mu.g.	34.degree.
Bombesin	7 picomoles	34.7.degree.
	20 picomoles	33.8.degree.
	70 picomoles	33.degree.
	7 nanomoles	32.1.degree.
No. 1	10 picomoles	34.3.degree.. . .

DETDESC:

DETD(24)

Following . . . of glucose were determined using a Beckman glucose analyzer. The results in causing a rise in plasma glucose relative to **Bombesin** are set forth hereinafter in Table III.

DETDESC:

DETD(25)

TABLE III

PEPTIDE	POTENCY (Plasma Glucose)
Bombesin	100
No. 1	100
No. 2	150
No. 3	150

US PAT NO: 4,253,998 [IMAGE AVAILABLE] L1: 32 of 45
DATE ISSUED: Mar. 3, 1981
TITLE: Peptides related to **somatostatin**
INVENTOR: Dimitrios Sarantakis, West Chester, PA
ASSIGNEE: American Home Products Corporation, New York, NY (U.S. corp.)
APPL-NO: 06/019,216
DATE FILED: Mar. 9, 1979
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Arthur G. Seifert

US PAT NO: 4,253,998 [IMAGE AVAILABLE] L1: 32 of 45

ABSTRACT:
Peptides of the formula: ##STR1## wherein: X is H, --NH.sub.2, --NH--Gly--Ala, --NH--D--Ala--Ala, --NH--Gly--Gly--Gly, --NH--acetyl, or --NH--benzoyl;
X.sub.1 is His or Arg;
X.sub.2 is His, Glu, Tyr, Trp, or Phe;
X.sub.3 is Trp, D-Trp, or 6-F-D-Trp; and
X.sub.4 is a D-.alpha.-amino acid;
or the reduced, linear form thereof, or a non-toxic, pharmaceutically acceptable acid addition salt thereof; inhibit the release of growth hormone, insulin, and glucagon; and show prolonged inhibition activity. Said peptides are prepared by solid-state methodology.
TITLE: Peptides related to **somatostatin**

SUMMARY:

BSUM(1)

This invention related to synthetic peptides structurally related to **somatostatin** and to intermediates employed in the synthesis thereof. In the compounds of the invention, the **somatostatin** peptide chain is modified at the 4, 5, and 13 position, with the 1, 2, 8, and 14 positions being. . .

SUMMARY:

BSUM(2)

Somatostatin is the cyclic disulfide tetradecapeptide of the formula: ##STR2## This peptide (I) has been identified as the "somatotropin-release inhibiting factor". . . (USA), 70, 684 (1973), and Ling et al., Biochemical and Biophysical Res. Communication, 50, 127 (1973)]. The reduced form of **somatostatin** (RS) is the linear tetradecapeptide of the formula: ##STR3##

SUMMARY:

BSUM(3)

The . . . (1973) and Sarantakis and McKinley, Biochem. and Biophys. Res. Communications, 54, 234 (1973)] and it (II) can be converted to **somatostatin** (I) by oxidation whereby a bridging bond is formed between the two sulfhydryls of the two cysteinyl amino acid residues. . .

SUMMARY:

BSUM(4)

Various polypeptides which may be regarded as structural modifications of **somatostatin** have been prepared synthetically and are reported in the chemical literature. Such polypeptides have certain structural features in common with **somatostatin** and differ from **somatostatin** in that specific amino acid residues or functional groups originally present in the **somatostatin** molecule are either missing or are replaced by other amino acid residues or functional groups. The present invention relates to novel synthetic biologically active polypeptides which may be regarded as a structural modification of **somatostatin**. The polypeptides of the invention differ from **somatostatin** in the following respects:

SUMMARY:

BSUM(11)

(g) the Cys.sup.14 residue is either present or replaced by D-Cys. Modifications of **somatostatin** missing the Ala.sup.1 -Gly.sup.2 segment and the N-terminal amino group are reported by Rivier et al., J. Med. Chem., 18,. . . the Trp.sup.8 residue by D-Trp is discussed by Rivier et al., Biochem. Biophys. Res. Commun., 65, 746 (1975). Modifications of **somatostatin** wherein the Lys.sup.4 -Asn.sup.5 segment are replaced with other amino acid residues are disclosed in Belgian Pat. 839,405. A modification of **somatostatin** wherein D-serine is substituted for Ser.sup.13 is described by Coy et al., "58th Annual Meeting of the Endocrine Society," San Francisco, California, Abstract 305, page 209. D-Trp.sup.8, D-Cys.sup.14 -**Somatostatin** is described by Brown et al., Science, 196, 1467 (1977) and Meyer, Biochem. Biophys. Res. Commun., 74, 630 (1977).

SUMMARY:

BSUM(21)

It . . . apparent to those skilled in the art that the .alpha.-carbon of the cysteine residues (corresponding to Cys.sup.3 and Cys.sup.14 of **somatostatin**) contain an assymetric carbon atom and optical isomers of such amino acid residues are possible. In the peptides depicted by. . .

DETDESC:

DETD(31)

A . . . to yield crude product, which was applied to a column of Sephadex G-25 (2.5.times.160 cm.) and eluted with 10% aq. **acetic** **acid**. Fractions 113 to 133 were collected and **lyophilized** to yield the title **peptide**, 855 mg.

US PAT NO: 4,244,947 [IMAGE AVAILABLE] L1: 33 of 45
DATE ISSUED: Jan. 13, 1981
TITLE: Carba decapeptide derivatives of [TYR.sup.6]-**somatostatin**
INVENTOR: Nedumparampil A. Abraham, Dollard des Ormeaux, Canada
Francesco Bellini, Mount Royal, Canada
Hans U. Immer, Mount Royal, Canada
Marvin M. Kobric, St. Laurent, Canada
ASSIGNEE: Ayerst McKenna and Harrison Inc., Montreal, Canada (foreign corp.)
APPL-NO: 06/066,258
DATE FILED: Aug. 13, 1979
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Arthur E. Wilfond

US PAT NO: 4,244,947 [IMAGE AVAILABLE] L1: 33 of 45

ABSTRACT:
Peptides of formula I ##STR1## in which X is (CH.sub.2).sub.2, S--CH.sub.2 or CH.sub.2 --S or a therapeutically acceptable acid addition salt thereof are disclosed. The peptides of formula I are useful as agents for the treatment of acromegaly and the management of diabetes in a mammal. Compositions and methods for the preparation of the peptides of formula I are also disclosed.
TITLE: Carba decapeptide derivatives of [TYR.sup.6]-**somatostatin**

SUMMARY:

BSUM(3)

This invention relates to carba derivatives of the tetradecapeptide **somatostatin**. More particularly, this invention concerns carba decapeptide derivatives in which phenylalanine at position 6 is replaced with tyrosine, the L-tryptophan. . .

SUMMARY:

BSUM(5)

The name "**somatostatin**" has been proposed for the factor found in hypothalamic extracts which inhibits the secretion of growth hormone (somatotropin). The structure. . .

SUMMARY:

BSUM(6)

The constitution of the tetradecapeptide **somatostatin** has been confirmed by synthesis; for example, see D. Sarantakis and W. A. McKinley, Biochem. Biophys. Res. Comm., 54, 234. . .

SUMMARY:

BSUM(8)

Since the structure and physiological activity of **somatostatin** were determined, a number of analogs of **somatostatin** have been reported, for instance see the report by J. Rivier, et al., in "Peptides 1976", Editions de L'Universite de Bruxelles, Brussels, Belgium, edited by A. Loffet, 1977, pp. 427-451. More specifically, a number of decapeptide derivatives of **somatostatin** have been reported, for example: Derwent Publications Ltd., Farmdoc 75059X for Netherland patent application Ser. No. 7,602,395, published Sept. 14,. . .

SUMMARY:

BSUM(9)

Carba decapeptide derivatives of **somatostatin** also are known; for example, Derwent Publications Ltd., Farmdoc 13282Y for German patent application No. 2,635,558, published Feb. 17, 1977. . .

SUMMARY:

BSUM(10)

Furthermore, a number of **somatostatin** derivatives in which a phenylalanine residue is replaced by a tyrosine residue is reported by J. E. Rivier et al.,. . .

SUMMARY:

BSUM(11)

The present invention discloses novel carba decapeptide derivatives of **somatostatin** in which phenylalanine at position 6 is replaced with tyrosine, the L-tryptophan is replaced with D-tryophan and one or two. . . These decapeptides show a greater inhibition on the release of glucagon than on the release of insulin when compared to **somatostatin**. This feature makes the decapeptides of this invention especially useful for the treatment of diabetes in a diabetic mammal.

SUMMARY:

BSUM(49)

The peptide of formula I or **somatostatin** at various concentrations is infused simultaneously with the arginine or glucose stimulus, with the aid of a butterfly infusion set. . .

SUMMARY:

BSUM(53)

Table I indicates that **somatostatin** suppresses IRI at a lower dose than does the peptide of formula I in which X is (CH.sub.2).sub.2.

SUMMARY:

BSUM(54)

Table II illustrates the IRG responses to the infusion of arginine in the absence and in the presence of peptides. Both **somatostatin** and the peptide of formula I in which X is (CH.sub.2).sub.2 suppresses the IRG secretion about equally.

SUMMARY:

BSUM(55)

Table III illustrates that **somatostatin** is significantly more potent than the peptide of formula I in which X is (CH.sub.2).sub.2 in suppressing IRI secretion on. . .

SUMMARY:

BSUM(59)

TABLE I

The effects of **somatostatin** and the peptide of formula I in which X is (CH.sub.2).sub.2 on arginine stimulated insulin secretion

Treatment	Dose.sup.1	.DELTA.IRI(.mu.U/ml).sup.2,5. . .	p.sup.3
Study A			
vehicle	--	4.7 .+-. 0.6(12).sup.4	--
arginine	--	80.2 .+-. 22.9(6)	--
arginine + **somatostatin**			
	0.3	73.8 .+-. 18.5(6)	NS
	1.0	43.0 .+-. 22.6(6)	NS
	3.0	40.0 .+-. 6.6(6)	
. . .			NS
Study B			
vehicle	--	6.9 .+-. 9.1(12)	--
arginine	--	77.6 .+-. 5.2(12)	--
arginine + **somatostatin**			
	0.03	88.3 .+-. 9.1(6)	NS
	0.3	76.8 .+-. 5.2(5)	NS
	3.0	32.2 .+-. 3.5(6)	
. . .			NS
Study C			
vehicle	--	25.2 .+-. 5.5(6)	--
arginine	--	101.7 .+-. 21.2(6)	--

arginine + **somatostatin**
10.0 52.8 .+-. 9.3(6)
<0.05
100.0 25.5 .+-. 8.1(6)
<0.01
arginine + peptide.sup.6
10.0 93.8. . .

SUMMARY:

BSUM(60)

TABLE II

The effect of **somatostatin** and the peptide of formula I in which X is (CH.sub.2).sub.2 on arginine stimulated glucagon secretion

Treatment	Dose.sup.1	.DELTA.IRG(pg/ml).sup.2,5. . .	p.sup.3
Study A			
vehicle	--	-1.8 .+-. 7.7(12).sup.4	
		--	
arginine	--	268.5 .+-. 18.4(12)	
		--	
arginine + **somatostatin**			
	0.3	157.2 .+-. 35.9(6)	
		<0.05	
	1.0	72.7 .+-. 19.0(6)	
		<0.01	
	3.0	102.5 .+-. 25.8(6)	
. . .			
		<0.01	
Study B			
vehicle	--	17.8 .+-. 3.6(12)	
		--	
arginine	--	229.9 .+-. 21.8(12)	
		--	
arginine .+-. **somatostatin**			
	0.03	211.0 .+-. 23.1(4)	
		NS	
	0.3	149.2 .+-. 29.9(6)	
		NS	
	3.0	69.3 .+-. 22.2(6)	
. . .			

SUMMARY:

BSUM(61)

TABLE III

The effect of **somatostatin** and the peptide of formula I in which X is (CH.sub.2) .sub.2 on glucose stimulated insulin secretion

Treatment	Dose.sup.1	IRI/ml.sup.2	p.sup.3

Study A			
glucose	--	77.2 .+-. 13.5(6).sup.4	
			--
glucose + **somatostatin**			
	10	27.2 .+-. 4.7(6)	
			<0.05
	100	12.3 .+-. 3.9(6)	
			<0.01
glucose + peptide.sup.5			
	10	47.2. . .	
			0.01
Study B			
vehicle	--	9.3 .+-. 2.1(6)	
			--
glucose	--	89.2 .+-. 8.4(6)	
			--
glucose + **somatostatin**			
	10	40.3 .+-. 7.7(6)	
			<0.01
	30	17.0 .+-. 7.5(6)	
			<0.01
	100	6.2 .+-. 1.9(6)	

. . .

SUMMARY:

BSUM(76)

The free base of the **peptide** of formula I can be obtained by repeated **lyophilization** of the **acetic** **acid** addition salt of the **peptide** of formula I from water.

US PAT NO: 4,225,472 [IMAGE AVAILABLE] L1: 34 of 45
DATE ISSUED: Sep. 30, 1980
TITLE: Truncated **somatostatin** analogs
INVENTOR: Dimitrios Sarantakis, West Chester, PA
ASSIGNEE: American Home Products Corporation, New York, NY (U.S. corp.)
APPL-NO: 06/042,842
DATE FILED: May 29, 1979
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Richard K. Jackson

US PAT NO: 4,225,472 [IMAGE AVAILABLE] L1: 34 of 45

ABSTRACT:
Polypeptides of the formula: ##STR1## in which X.sub.1 is hydrogen, des-amino, Ala-Gly- or Ala-D-Ala;
X.sub.2 is Trp, Leu, Met or p-Cl-Phe; and
X.sub.3 is D-Trp or 5- or 6-fluoro-D-Trp;
the linear precursor intermediates thereof or pharmaceutically acceptable salts thereof are selective inhibitors of growth hormone and glucagon release without materially altering blood serum levels of insulin.
TITLE: Truncated **somatostatin** analogs

SUMMARY:

BSUM(10)
and . . . atoms; or a pharmaceutically acceptable salt thereof. These compounds, while possessing the common ability to suppress growth hormone, differ from **somatostatin** in their selective activity toward growth hormone and glucagon without suppression of insulin, in their long term biological activity and structurally in that they omit the amino acid residues of Lys.sup.4, Asn.sup.5, Thr.sup.12 and Ser.sup.13 of **somatostatin** and replace Phe.sup.7 with Trp, Leu, Met or P-Cl-PHe; Trp.sup.8 with D-Trp or 5- or 6-fluoro-D-Trp and Cys.sup.14 with D-Cys. In addition, the amino acid moieties appearing in 1- and 2-positions of **somatostatin** are either present as Ala-Gly- or they may be substituted with Ala-D-Ala, entirely omitted with or without the presence of. . .

DETDESC:

DETD(31)

The . . . Bio-Rad AG3-X4A (100 g.) for 30 minutes and filtered. The filtrate was passed through Amberlite CG-50 (H+form) and the absorbed **peptide** was eluted with 50% aqueous **acetic** **acid**. The fractions containing the peptidic material were pooled and **lyophilized** to yield 1.1 g. of crude material. This crude product was chromatographed through a column of Sephadex G-25 (2.5 cm..times.150. . .

US PAT NO: 4,212,795 [IMAGE AVAILABLE] L1: 35 of 45
DATE ISSUED: Jul. 15, 1980
TITLE: Cyclization of peptides
INVENTOR: John L. Hughes, Kankakee, IL
Jay K. Seyler, Bourbonnais, IL
Robert C. Liu, Kankakee, IL
ASSIGNEE: Armour Pharmaceutical Company, Kankakee, IL (U.S. corp.)
APPL-NO: 05/960,229
DATE FILED: Nov. 13, 1978
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Carl C. Batz

US PAT NO: 4,212,795 [IMAGE AVAILABLE] L1: 35 of 45

ABSTRACT:
The synthesis of a disulfide cyclic peptide by preparing an intermediate peptide containing two cysteine moieties, each of which is protected by an n-alkylthio group, or when one of such moieties is in an amino terminal position, this one moiety may be protected by a cysteine group while the other is protected by an n-alkylthio group, and placing such intermediate peptide in a solution substantially free of oxygen and preferably at a pH of from 5 to 10 until rearrangement has taken place, to yield a cyclic disulfide peptide. The disclosure also embraces said intermediate peptides as new compounds and the processes by which they are prepared.

SUMMARY:

BSUM(31)

TABLE IX

Position Number	Typical Reactants For Use In The Synthesis of **Somatostatin** Amino Acid Reactant
14	BOC-S-methylthio-L-cysteine, BOC-S-ethylthio-L-cysteine, BOC-S-n-propylthio-L-cysteine, or BOC-S-n-butylthio-L-cysteine
13	BOC-O-benzyl-L-serine
12	BOC-O-benzyl-L-threonine
11. . .	

DETDESC:

DETD(172)

The . . . 4.times.25 ml portions of ethyl acetate. The peptide was extracted from the resin beads with 2=50 ml portions of glacial **acetic** **acid**. The extract was **lyophilized** to the cleaved **peptide**.

DETDESC:

DETD(273)

The . . . with 2.times.25 ml portions of ehtyl acetate. The peptide was extracted from the resin beads with 2.times.50 ml of glacial **acetic** **acid**. The extract was **lyophilized** to give the cleaved **peptide**.

DETDESC:

DETD(293)

In the synthesis of **somatostatin**, the amino acid sequence of **somatostatin** may be prepared using the amino acid derivatives described in Table IX or equivalents thereof. The formuli for the precursor. . .

DETDESC:

DETD(294)

After . . . acid treatment to cleave the resin and acid labile protective groups, the formuli becomes: ##STR35## which is a precursor of **somatostatin**.

DETDESC:

DETD(295)

After subjecting this peptide to our disulfide bond rearrangement procedure as herein described, the peptide becomes: ##STR36## which is **somatostatin**.

CLAIMS:

CLMS(18)

18. A peptide as set forth in claim 13 in which said amino acid sequence is the same as that of **somatostatin**.

US PAT NO: 4,204,990 [IMAGE AVAILABLE] L1: 36 of 45
DATE ISSUED: May 27, 1980
TITLE: **Somatostatin** analogues
INVENTOR: Dimitrios Sarantakis, West Chester, PA
ASSIGNEE: American Home Products Corporation, New York, NY (U.S. corp.)
APPL-NO: 05/895,577
DATE FILED: Apr. 12, 1978
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Richard K. Jackson

US PAT NO: 4,204,990 [IMAGE AVAILABLE] L1: 36 of 45

ABSTRACT:
Polypeptides of the formula: ##STR1## the linear precursors and non-toxic acid addition salts thereof, wherein: R is hydrogen, lower alkanoyl, benzoyl, Ala-Gly-, Gly-Gly-Gly-, Ala-D-Ala- or p-Glu;
X.sub.4 is Arg or Lys;
X.sub.5 is a D-.alpha.-amino acid;
X.sub.8 is L-Trp or D-Trp; and
X.sub.14 is Cys or D-Cys
are described. These **somatostatin** analogues are useful as inhibitors of growth hormone and insulin secretion, selectively inhibiting growth hormone, insulin and glucagon and they demonstrate prolonged growth hormone inhibition for periods exceeding two hours. The compounds of this invention are useful in the treatment of diabetes, acromegaly and other dysfunctions characterized by excessive secretion of growth hormone and/or insulin.
TITLE: **Somatostatin** analogues

ABSTRACT:
Polypeptides . . .
is Arg or Lys;
X.sub.5 is a D-.alpha.-amino acid;
X.sub.8 is L-Trp or D-Trp; and
X.sub.14 is Cys or D-Cys
are described. These **somatostatin** analogues are useful as inhibitors of growth hormone and insulin secretion, selectively inhibiting growth hormone, insulin and glucagon and they. . .

SUMMARY:

BSUM(14)

These compounds inhibit the secretion of growth hormone, insulin and in some cases, glucagon, demonstrating prolonged growth hormone suppression, and like **somatostatin**, they are useful in the treatment of diabetes mellitus, acromegaly, and other diseases characterized by excessive secretion of growth hormone. . .

DETDESC:

DETD(25)

To demonstrate prolonged activity of the compounds of this invention, [des-Ala.sup.1 -Gly.sup.2],Arg.sup.4, D-Tyr.sup.5, D-Trp.sup.8, D-Cys.sup.14 -**somatostatin**, as a representative compound of the invention, was administered (SC) to nonfasted male Charles River CD.RTM. rats with vehicle administration. . .

DETDESC:

DETD(27)

Thus, [des-Ala.sup.1 -Gly.sup.2], Arg.sup.4, D-Tyr.sup.5, D-Trp.sup.8, D-Cys.sup.14 -**Somatostatin**, representative of the other compounds of the invention is an effective agent for reducing secretion of growth hormone, insulin, and. . .

DETDESC:

DETD(32)

The . . . 70 g. of ion exchange resin Bio Rex-70 (cationic form) and the resin was washed with water, then the absorbed **peptide** was eluted with a mixture of pyridine-water-**acetic** **acid**, 30:4:60, v/v. The fractions containing the **peptide** were **lyophilized** to afford 1.8 g. of crude **peptide**. This crude **peptide** was chromatographed through a column of Sephadex G-15 (2.5.times.120 cm) and eluted with 10% aq. AcOH. Fractions of 5.5 ml.. . .

US PAT NO: 4,190,575 [IMAGE AVAILABLE] L1: 37 of 45
DATE ISSUED: Feb. 26, 1980
TITLE: Polypeptides related to **somatostatin**
INVENTOR: Dimitrios Sarantakis, West Chester, PA
ASSIGNEE: American Home Products Corporation, New York, NY (U.S. corp.)
APPL-NO: 05/864,173
DATE FILED: Dec. 27, 1977
ART-UNIT: 125
PRIM-EXMR: Delbert R. Phillips

US PAT NO: 4,190,575 [IMAGE AVAILABLE] L1: 37 of 45

ABSTRACT:
Compounds of the formula: ##STR1## wherein: X is H, Ala-Gly, Gly-Gly-Gly, Ala-D-Ala, acetyl, or benzoyl;
X.sub.1 is Arg or His;
X.sub.2 is Glu or Asp;

X.sub.3 is Trp or D-Trp; or 6-F-D-Trp; and
X.sub.4 is Cys- or D-Cys; or
a non-toxic pharmaceutically acceptable acid addition salt thereof; inhibit the secretion of growth hormone and glucagon without materially affecting the secretion of insulin.
TITLE: Polypeptides related to **somatostatin**

SUMMARY:

BSUM(1)

Somatostatin is the cyclic disulfide tetradecapeptide of the formula: ##STR2## This peptide (I) has been identified as the "somatotropin-release inhibiting factor". . . (USA), 70, 684 (1973), and Ling et al., Biochemical and Biophysical Res. Communication, 50, 127 (1973)]. The reduced form of **somatostatin** (RS) is the linear tetradecapeptide of the formula: ##STR3##

SUMMARY:

BSUM(2)

The . . . 2737 (1973) and Sarantakis and McKinley, Biochem. and Biophys. Res. Communications, 54, 234 (1973)]and it (II) can be converted to **somatostatin** (I) by oxidation whereby a bridging bond is formed between the two sulfhydryls of the two cysteinyl amino acid residues. . .

SUMMARY:

BSUM(3)

Various polypeptides which may be regarded as structural modifications of **somatostatin** have been prepared synthetically and are reported in the chemical literature. Such polypeptides have certain structural features in common with **somatostatin** and differ from **somatostatin** in that specific amino acid residues or functional groups originally present in the **somatostatin** molecule are either missing or are replaced by other amino acid residues or functional groups. The present invention relates to novel synthetic biologically active polypeptides which may be regarded as a structural modification of **somatostatin**. The polypeptides of the invention differ from **somatostatin** in the following respects:

SUMMARY:

BSUM(7)

(d) the Trp.sup.8 residue is either present or replaced by D-Trp or 6-F-D-Trp. Modifications of **somatostatin** missing the Ala.sup.1 -Gly.sup.2 segment and the N-terminal amino group are reported by Rivier et al., J. Med. Chem., 18,. . . the Trp.sup.8 residue by D-Trp is discussed by Rivier et al., Biochem. Biophys. Res. Commun., 65, 746 (1975). Modifications of **somatostatin** wherein the Lys.sup.4 -Asn.sup.5 segment are replaced with other amino acid residues are disclosed in Belgian Patent No. 839,405. **Somatostatin** derivatives where the Asn.sup.5 residue is replaced by Asp are described in Belgian

Patent No. 827,530.

DETDESC:

DETD(31)

The . . . mg. of material. This material was applied onto a column of Sephadex G25 (1.5.times.115 cm.) and eluted with 10% aq. **acetic** **acid**. The fractions 43-53 were pooled and **lyophilized** to give the title **peptide**, 286 mg.

US PAT NO: 4,145,337 [IMAGE AVAILABLE] L1: 38 of 45
DATE ISSUED: Mar. 20, 1979
TITLE: Aminoethylglycine containing polypeptides
INVENTOR: Wallace M. Dairman, Monsey, NY
Arthur M. Felix, West Caldwell, NJ
Hugo E. Gallo-Torres, Livingston, NJ
Edgar P. Heimer, Sparata, NJ
Johannes A. Meienhofer, Upper Montclair, NJ
ASSIGNEE: Hoffmann-La Roche Inc., Nutley, NJ (U.S. corp.)
APPL-NO: 05/840,922
DATE FILED: Oct. 11, 1977
ART-UNIT: 124
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Jon S. Saxe, George M. Gould

US PAT NO: 4,145,337 [IMAGE AVAILABLE] L1: 38 of 45

ABSTRACT:
Novel **somatostatin** analogues containing one or more aminoethylglycyl residues at the amino and/or carboxyl terminus or in the ring position are described. The compounds are potent and long lasting inhibitors of gastric acid secretion.

ABSTRACT:
Novel **somatostatin** analogues containing one or more aminoethylglycyl residues at the amino and/or carboxyl terminus or in the ring position are described.. . .

SUMMARY:

BSUM(2)

The structure of the growth hormone release inhibiting factor, **somatostatin** (GH-RIH; SRIF) has been determined by Brazeau et al., Science 179, 77 (1973). Several techniques for synthesizing **somatostatin** have been reported in the literature, including the solid phase method of Rivier, J. A. C. S., 96, 2986 (1974). . .

SUMMARY:

BSUM(3)

The preparation of **somatostatin** and acylated des-(Ala.sup.1, Gly.sup.2) derivatives is described in U.S. Pat. No. 3,904,594.

SUMMARY:

BSUM(4)

Bloom et al. Lancet, II, 1106 (1974) have shown that **somatostatin** inhibits basal gastric secretion and gastrin release. Subcutaneous administration of **somatostatin** in rats has been shown to have prophylactic effect on restraint ulcer formation (Zierden et al., Res. Exp. Med., 168, 199 (1976). Infusion of **somatostatin** in man has been reported to stop peptic ulcer bleeding (Rasche et al, Klin, Wschr., 54, 977 (1976). However, the inhibitory effects of **somatostatin** on gastric secretion (chronic fistula dog) were shown to be of short duration (Torchiana et al, Proc. Soc. Exp. Biol. Med., 154, 449 [1977]). Thus in order to have clinical therapeutic value, new analogs of **somatostatin** are believed to be required which analogs would have long lasting and specific acitivity. A number of analogs of **somatostatin** have been prepared and are described in the scientific and patent literature. A summary of such references follows:

SUMMARY:

BSUM(5)
(D-Trp.sup.8)-**Somatostatin**--Rivier et al, Biochem. Biophys. Res. Comm., 65, 746 (1975)

SUMMARY:

BSUM(6)
(Ala.sup.3 --Ala.sup.14)-**Somatostatin** --U.S. Pat. No. 3,842,066

SUMMARY:

BSUM(7)
Des (Ala.sup.1, Gly.sup.2, Asn.sup.5)-**Somatostatin**-- U.S. Pat. No. 3,882,098

SUMMARY:

BSUM(8)
Derivatives of **Somatostatin**-- U.S. Pat. No. 3,917,581

SUMMARY:

BSUM(9)
A cyclic undecapeptide **Somatostatin** analog-- Sarantakis et al., Biochem. Biophys. Res. Comm. 73 336 (1976)

SUMMARY:

BSUM(10)
Des(Ala.sup.1 Gly.sup.2)--desamino (Cys.sup.3) descarboxy(Cys.sup.14) dicarba.sup.3,14 -**Somatostatin**--Veber et al., J. A. C. S. 98 2367 (1976)

SUMMARY:

BSUM(11)

Cyclic Dodecapeptide Analogs of **Somatostatin**--U.S. Pat. No. 4,000,259

SUMMARY:

BSUM(12)
Des (Ser.sup.13)-**Somatostatin**--U.S. Pat. No. 3,933,784

SUMMARY:

BSUM(13)
(Tyr.sup.3, Tyr.sup.14)--**Somatostatin**--U.S. Pat. No. 3,988,308

SUMMARY:

BSUM(14)
Cyclic **Somatostatin** Disulfide Analogs-- U.S. Pat. No. 3,997,517

SUMMARY:

BSUM(15)
(Acyl-D-.alpha.-amino acid -Gly-Gly-Tyr-Ala).sup.1 -**Somatostatin**--
U.S. Pat. No. 3,988,795

SUMMARY:

BSUM(21)
It is further of interest to not that while the (D-Trp.sup.8)-
somatostatin analog exhibits higher potency than **somatostatin** in inhibition of growth hormone, insulin and glucagon, that analog is less potent in inhibition of pentagastrin-induced gastric acid secretion.. . .

SUMMARY:

BSUM(23)

The present invention relates to novel anlaogs of **somatostatin** which contain one or more aminoethylglycine (Aeg) residues at the amino and/or carboxyl-terminals or in the ring position. The compounds. . .

SUMMARY:

BSUM(41)

The . . . formula II having a free amino terminal (R.sup.1 =H) are particularly useful for the synthesis of the novel NH.sub.2 -terminal Aeg-**somatostatin** analogs of formula I. Such analogs may be conveniently prepared by coupling a compound of formula II with a suitable. . .

DETDESC:

DETD(66)

The . . . a wash. The Bio-Rex 70 column (0.8 .times. 12 cm.) was washed with 5% acetic acid (50 ml.) and the **peptide** displaced with 50% **acetic** **acid**. Fractions 1-8 (0-18 ml.) were **lyophilized**

and purified by gel filtration on a 0.9 .times. 54 cm Sephadex G-25 column. Fractions 10-16 (20-32 ml.) gave a. . .

DETDESC:

DETD(153)

A. Gastric Antisecretory Activity of **Somatostatin** Analogs

DETDESC:

DETD(154)

The gastric antisecretory effect of **somatostatin** analogs was studied in a model which utilizes unanesthetized rats. The test compounds are shown in the following table.

DETDESC:

DETD(155)

SOMATOSTATIN ANALOGS CONTAINING AMINOETHYLGLYCINE (Aeg)

DETDESC:

DETD(164)

(a) The reduced form of **somatostatin** (Compound B) is as active as the oxidized, cyclic **somatostatin** (Compound A).

DETDESC:

DETD(165)

(b) . . . of Aeg to the C-terminal, as in Compound I and Compound J, results in compounds which are less active than **somatostatin**.

DETDESC:

DETD(166)

(c) The novel carba-**somatostatin** analog which contains Aeg in the ring portion (Compound D) exhibits erratic activity.

DETDESC:

DETD(169)

(f) . . . biological activity and signaificantly longer duration of effect is observed by the combination of more than one substitution in the **somatostatin** molecule, as in Compound L and its oxidized form, Compound M.

DETDESC:

DETD(171)

With a few exceptions, those compounds which were more active than **somatostatin** in terms of increasing pH and decreasing total gastric acid concentration were also more active in inhibiting the volume as. . .

DETDESC:

DETD(173)

Stimulation . . . initial studies were carried out to explore the possibility that analogs such as Compound M, which are more active than **somatostatin**, may have an effect on gastric mucus production.

DETDESC:

DETD(178)

These data suggest that certain analogs of **somatostatin** with high antisecretory activity of longer duration of action, such as Compound M, are also capable of provoking an enhancement. . .

DETDESC:

DETD(180)

Recently, Zierden and his colleagues (Res. Exp. Med. 168: 199-201, 1976) studied the possible prophylactic effect of **somatostatin** on stress ulcer formation. The method employed consisted of restraining rats by the standard effectively prevented the formation of of. . . as well as 3 h and 6 h later, animals (means body weight = 192 g) received subcutaneous injection of **somatostatin** (100 .mu.g linear protamine-zinc-**somatostatin**/rat). Rats treated with **somatostatin** before and during stress had only 1/5 of the ulcers of the untreated animals after 9 hours of immobilization. In cats, **somatostatin**, administered by continuous intravenous infusion in graded doses (range: 0.62 to 5.0 .mu.g/kg-hr) effectively prevented the formation of duodenal ulcers. . . is the work of Mattes, et al. (Horm. Metab. Res. 7: 508-511, 1975) who reported their results of an extended **somatostatin** treatment in a 65 year-old male patient with heavy gastrointestinal bleeding on the 9th postoperative day following a high Billroth. . . be caused by two residual ulcers in the area of the anastomosis. A dose of 250 .mu.g of synthetic cylic **somatostatin** was administered i.v. as a bolus. This was followed by an infusion of 250 .mu.g per hour for 67 hours. **Somatostatin** treatment led to an immediate cessation of the bleeding after 1 hour. Endoscopy at the end of treatment period showed. . .

DETDESC:

DETD(181)

Since the above reports suggest that **somatostatin** may possess antiulcerogenic activities, it was of interest to explore the effects of some of the derivatives of **somatostatin** containing Aeg. In both studies CD-1 male mice weighing between 18-25 g were used. The mice were fasted for 19. . . the initiation of the restraint-immersion procedure, mice received, via the subcutaneous route, graded amounts (0.1 to 10 mg/kg b.w.) of **somatostatin** (Compound A), Compound F, or

vehicle (5% acacia); this administration was repeated two hours later. In the second study, the. . . the probit method of Finney (Finney, "Probit Analysis", Cambridge University Press, 1971). The comparative effectiveness (relative potency R. P.) of **somatostatin** and Compound F (first study) or **somatostatin** and Compound L (second study) was determined from the dose responses using an "ED50" computer program.

DETDESC:

DETD(182)

In the first study, both **somatostatin** and the **somatostatin** anlaog Compound F were found to be effective in preventing restraint-immersion induced gastric ulceration in the mouse; Compound F was ca 5.6-fold less potent that **somatostatin**. The respective ED50 values for Compound F and **somatostatin** were 1.93 and 0.35 mg/kg. The second study demonstrated that Compound L was ca. 4.6-fold more potent than **somatostatin**. This value was based on the computer generated term R. P. (relative potency), an analysis which considers the entire dose. . . response curve. However, on the basis of ED50 values, Compound L was found to be ca. 6.8-fold more potent than **somatostatin** (see Table 2).

DETDESC:

DETD(183)

Somatostatin analogs with high and prolonged antisecretory activity, such as Compound L, are also more potent inhibitors of restraint-immersion ulcer formation than **somatostatin**. These results suggest that certain **somatostatin** analogs could be useful in the treatment of peptic ulceration.

DETDESC:

DETD(184)

Table 2

ANTI-ULCEROGENIC ACTIVITY OF **SOMATOSTATIN** AND COMPOUND L IN THE MOUSE RESTRAINT-IMMERSION TEST

	ED50 (mg/kg)
Somatostatin (Compound A)	6.70
Compound L	0.98

US PAT NO: 4,118,380 [IMAGE AVAILABLE] L1: 39 of 45
DATE ISSUED: Oct. 3, 1978
TITLE: Decapeptide analogs of **somatostatin**
INVENTOR: Hans U. Immer, Mount Royal, Canada
Nedumparambil A. Abraham, Dollard des Ormeaux, Canada
ASSIGNEE: Ayerst, McKenna & Harrison Limited, Montreal, Canada (foreign corp.)

APPL-NO: 05/818,500
DATE FILED: Jul. 25, 1977
ART-UNIT: 124
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Stephen Venetianer

US PAT NO: 4,118,380 [IMAGE AVAILABLE] L1: 39 of 45

ABSTRACT:
Compounds of the formula 1 or 1a ##STR1##

HSCH.sub.2 CH.sub.2 CO-A-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-NHCH.sub.2 CH.sub.2 SH (1a)
in which A is Gly-Asn or Lys-Gly, or therapeutically acceptable salts thereof are disclosed. The compounds of formulae 1 and 1a are useful for the management of diabetes and the treatment of acromegaly in mammals. Compositions and methods for their use also are disclosed.
TITLE: Decapeptide analogs of **somatostatin**

SUMMARY:

BSUM(3)

This invention relates to derivatives of the tetradecapeptide **somatostatin**. More particularly, this invention concerns decapeptide derivatives in which Lys.sup.4 or Asn.sup.5 is replaced with a residue of glycine, salts. . .

SUMMARY:

BSUM(5)

The name "**somatostatin**" has been proposed for the factor found in hypothalamic extracts which inhibits the secretion of growth hormone (somatotropin). The structure. . .

SUMMARY:

BSUM(6)

The constitution of the tetradecapeptide **somatostatin** has been confirmed by synthesis; for example, see D. Sarantakis and W. A. McKinley, Biochem. Biophys. Res. Comm., 54, 234(1973),. . .

SUMMARY:

BSUM(8)

Since the structure and physiological activity of **somatostatin** was determined, a number of analogs of **somatostatin** have been reported, for instance see the report by J. Rivier et al., in "Peptides 1976", Editions de l'Universite de Bruxelles, Brussels, Belgium, edited by A. Loffet, 1977, 99. 427-451. More specifically, a number of shortened derivatives of **somatostatin** have been reported, for example: Netherlands patent application Ser. No. 7,602,395 published Sept. 14, 1976, discloses compounds of the formula. . .

SUMMARY:

BSUM(9)

The present invention discloses novel decapeptide derivatives of **somatostatin** in which Lys.sup.4 or Asn.sup.5 is replaced by a residue of glycine. Thus, these derivatives differ from the reported derivatives of **somatostatin** by having a different arrangement of amino acids. The derivatives of this invention possess a physiological activity similar to that of **somatostatin**. The derivatives are prepared readily by a convenient process, which includes the following advantages: the process starts from readily available. . .

SUMMARY:

BSUM(44)

The . . . as well as their corresponding therapeutically acceptable salts, are useful because they possess the pharmacological activity of the natural tetradecapeptide **somatostatin**. Their activity is demonstrated readily in pharmacological tests such as a modification [A. V. Schally et al., Biochem. Biophys. Res.. . .

SUMMARY:

BSUM(45)

The . . . al., cited above. In this test the peptides of this invention show a level of activity similar to that of **somatostatin**.

SUMMARY:

BSUM(70)

Finally, . . . addition salt with hydrochloric acid. In the case where Sephadex G-25 and acetic acid or acetic acid-water-butanol is employed, the **peptide** is obtained in the form of its **acetic** **acid** addition salt. The latter salt, when subjected to repeated **lyophilization** from water yields the cyclic decapeptide of formula 1 in which A is as defined herein in the form of. . .

US PAT NO: 4,055,553 [IMAGE AVAILABLE] L1: 40 of 45
DATE ISSUED: Oct. 25, 1977
TITLE: (Gly.sub.3 -Ala).sup.1 -**somatostatin**
INVENTOR: Sie-Yearl Chai, Royersford, PA
John P. Yardley, King of Prussia, PA
ASSIGNEE: American Home Products Corporation, New York, NY (U.S. corp.)
APPL-NO: 05/609,254
DATE FILED: Sep. 2, 1975
ART-UNIT: 124
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Richard K. Jackson

US PAT NO: 4,055,553 [IMAGE AVAILABLE] L1: 40 of 45

ABSTRACT:
The growth hormone release inhibiting compound: ##STR1## in which R is hydroxyl, dimethylamino, alkylamino of 1-5 carbon atoms or phenethylamine, the protamine zinc, protamine aluminum and non-toxic acid addition salts thereof as well as the corresponding linear heptadecapeptide and intermediates therefore are herein described.
TITLE: (Gly.sub.3 -Ala).sup.1 -**somatostatin**

SUMMARY:

BSUM(2)

The structure of the growth hormone release inhibiting factor, **somatostatin**, has been determined by Brazeau et al., Science, 179, 77(1973). Several techniques for synthesizing **somatostatin** have been reported in the literature, including the solid phase method of Rivier, J.A.C.S. 96, 2986(1974) and the solution methods. . .

SUMMARY:

BSUM(4)

In accordance with this invention, there is provided a growth hormone release inhibiting compound of the formula; (Gly.sub.3 --Ala).sup.1 -**Somatostatin**, and simple amides thereof as well as the non-cyclic form of the heptadecapeptide, the protamine zinc and protamine aluminum adducts,. . .

SUMMARY:

BSUM(7)

The deprotected linear heptadecapeptide and the corresponding amides are readily converted to the [6-17] cyclic disulfide (H-Gly-Gly-Gly-Ala).sup.1 -**Somatostatin** derivative by mild oxidation (e.g. air), preferably through exposure of a solution of the linear compound to atmospheric oxygen. The. . .

SUMMARY:

BSUM(20)

The in vivo activity of the compounds of this invention was established by subjecting (Gly.sub.3 -Ala).sup.1 -**Somatostatin**, as a representative compound of this invention, to the following standard test procedure: three groups of nine albino male rats were arranged to provide a control group, a group for observation of **Somatostatin** activity as the standard and a group for the study of the test compound (Gly.sub.3 -Ala).sup.1 -**Somatostatin**. Nembutal (50 mg/kg) was injected intraperitoneally into each rat. Fifteen minutes later a subcutaneous injection of the test compound, **somatostatin** (200 .mu.g/kg) and physiological saline was administered separately to each of the three groups of rats. Ten minutes later 0.5. . .

SUMMARY:

BSUM(21)

	Glucagon (pico- grams/ml) .mu.	Insulin units/ml	GH (ng/ml)
(Gly.sub.3 Ala).sup.1 -**Somatostatin**	0.5 .+-. 0.1	130 .+-. 14	
(100 .mu.g/kg) **Somatostatin**	1.5 .+-. 0.8	202 .+-. 29	
Saline	6.4 .+-. 1.5	199 .+-. 15	
(Gly.sub.3 -Ala).sup.1 -**Somatostatin**	1.4 .+-. 0.7	104 .+-. 10	27 .+-. 7
(300 .mu.g/kg) **Somatostatin**	1.6 .+-. 0.9	115 .+-. 11	12 .+-. 2
Saline	4.2 .+-. 0.6	165 .+-. 13	

. . .

SUMMARY:

BSUM(22)

Thus, the compounds of this invention (Gly.sub.3 -Ala).sup.1 -**Somatostatin** and the amides thereof are comparable in activity at the 100 and 300 .mu.g/kg dose levels to **somatostatin** itself and are effective substitutes for **somatostatin** in the treatment of diabetes mellitus and acromegaly, even though the heptadecapeptides of this invention contain more amino acid residues than **somatostatin**.

SUMMARY:

BSUM(23)

Administration of the heptadecapeptides of this invention may be by conventional routes common to **somatostatin** and related polypeptides, under the guidance of a physician, orally or parenterally, in an amount dictated by the extent of. . .

SUMMARY:

BSUM(38)

The . . . fluoride and the anisole are removed as quickly as possible under reduced pressure and the residue washed with ether. The **peptide** is dissolved in 10% **acetic** **acid** (degassed) and separated from the resin by filtration. **Lyophilization** yields the above titled product as white powder (860 mg.).

SUMMARY:

BSUM(41)

Thus, . . . (three times) and the combined filtrate and washings is concentrated in vacuo to yield the fully protected derivative of (Gly-Ala).sup.1 -**somatostatin**-HHC.sub.2 H.sub.5, which is treated with liquid HF (40 ml.) and anisole (9.3 ml.) in vacuo at ice bath temperature for. . . to the residue and extracted with diethyl ether. The combined aqueous layer is lyophilized to yield fully deprotected (Gly.sub.3 -Ala).sup.1 -**somatostatin**-NHC.sub.2 H.sub.5.

US PAT NO: 4,020,157 [IMAGE AVAILABLE] L1: 41 of 45
DATE ISSUED: Apr. 26, 1977
TITLE: Shortened analogs of **somatostatin**
INVENTOR: Nedumparambil A. Abraham, Dollard Des Ormeaux, Canada
Hans U. Immer, Mt. Royal, Canada
Verner R. Nelson, Kirkland, Canada
Kazimir Sestanj, Pointe Claire, Canada
ASSIGNEE: Ayerst McKenna and Harrison Ltd., Montreal, Canada
(foreign corp.)
APPL-NO: 05/594,159
DATE FILED: Jul. 8, 1975
ART-UNIT: 124
PRIM-EXMR: Lewis Gotts
ASST-EXMR: Reginald J. Suyat
LEGAL-REP: Stephen Venetianer

US PAT NO: 4,020,157 [IMAGE AVAILABLE] L1: 41 of 45

ABSTRACT:
Compounds of the formula 1 or 1a ##STR1##

HSCH.sub.2 CH(R)CO--Lys--Asn--Phe--Phe--Trp--Lys--Thr--Phe--Thr--Ser--NHCH.sub.2 CH.sub.2 SH (1a)

In which R is hydrogen or NHR.sup.1 in which R.sup.1 is lower aliphatic acyl containing from 1 - 6 carbon atoms or benzoyl, and pharmaceutically acceptable salts thereof are disclosed. The compounds of formulae 1 and 1a are useful for the management of diabetes and the treatment of acromegaly in mammals. Methods for their use also are disclosed.
TITLE: Shortened analogs of **somatostatin**

SUMMARY:

BSUM(3)

This invention relates to derivatives of the tetradecapeptide **somatostatin**. More particularly, this invention concerns shortened derivatives and salts thereof, a process for preparing said derivatives and salts, intermediates used. . .

SUMMARY:

BSUM(5)

The name "**somatostatin**" has been proposed for the factor found in hypothalamic extracts which inhibits the secretion of growth hormone (somatotropin). The structure. . .

SUMMARY:

BSUM(7)

The constitution of the tetradecapeptide **somatostatin** has been confirmed by synthesis; for example, see D. Sarantakis and W. A. McKinley, Biochem. Biophys. Res. Comm., 54 234. . .

SUMMARY:

BSUM(9)

The linear form of **somatostatin**, having two sulfhydryl groups instead of a disulfide bridge, has been prepared recently by J. E. F. Rivier, J. Amer. Chem. Soc., 96, 2986 (1974). He reports that the linear form is equipotent to **somatostatin** based on the ability of the two compounds to inhibit the rate of secretion of growth hormone by rat pituitary. . .

SUMMARY:

BSUM(10)

Only recently have there been reported polypeptides, other than the natural hormone and its linear form having **somatostatin**-like activity. D. Sarantakis et al., Biochem. Biophys. Res. Comm., 55, 538 (1973) recently reported the synthesis of the **somatostatin** analog, [Ala.sup.3,14]-**somatostatin**, by solid phase methods. This analog exhibited a very small amount of activity, about 0.01% of the potency of **somatostatin**. P. Brazeau et al., Biochem. Biophys. Res. Comm., 60, 1202 (1974) recently reported the synthesis of a number of acylated des-[Ala.sup.1 -Gly.sup.2]-**somatostatin** derivatives by solid phase methods.

SUMMARY:

BSUM(11)

The present invention discloses shortened chain derivatives of **somatostatin** which show a level of activity greater than or of the same order as the natural hormone as well as a duration of activity which is greater than that of **somatostatin**. Those derivatives are prepared readily by a convenient process, which includes the following advantages: the process starts from readily available. . .

SUMMARY:

BSUM(45)

The . . . as well as their corresponding pharmaceutically acceptable salts, are useful because they possess the pharmacological activity of the natural tetradecapeptide **somatostatin**. Their activity is demonstrated readily in pharmacological tests such as a modification [A.

V. Schally et al., Biochem. Biophys. Res.. . .

SUMMARY:

BSUM(46)

The . . . the peptides of this invention show a level of activity which is greater than or of the same order as **somatostatin**.

SUMMARY:

BSUM(62)

Finally, . . . addition salt with hydrochloric acid. In the case where Saphadex G-25 and acetic acid or acetic acid-water-butanol is employed, the **peptide** is obtained in the form of its **acetic** **acid** addition salt. The latter salt, when subjected to repeated **lyophilization** from water yields the cyclic undecapeptide of formula 1 (R = NHR.sup.1 and R.sup.1 is as defined above), for example. . .

US PAT NO: 4,010,260 [IMAGE AVAILABLE] L1: 42 of 45
DATE ISSUED: Mar. 1, 1977
TITLE: Derivatives of retro-enantio-**somatostatin**, intermediates therefor, and process therefor
INVENTOR: Hans U. Immer, Mount Royal, Canada
Nedumparambil A. Abraham, Dollard des Ormeaux, Canada
Verner R. Nelson, Kirkland, Canada
ASSIGNEE: Ayerst McKenna & Harrison Ltd., Montreal, Canada (foreign corp.)
APPL-NO: 05/599,448
DATE FILED: Jul. 28, 1975
ART-UNIT: 124
PRIM-EXMR: Lewis Gotts
ASST-EXMR: Reginald J. Suyat
LEGAL-REP: Stephen Venetianer

US PAT NO: 4,010,260 [IMAGE AVAILABLE] L1: 42 of 45

ABSTRACT:
Compounds of the formula 1 or 1a ##STR1## IN WHICH R is hydrogen or CONHCH.sub.2 CONHCH.sub.2 CH.sub.3 are disclosed. The compounds are obtained by a process which comprises the following step: preparing peptide fragments II, III, V and VII see below, by a series of condensations involving the reaction of an appropriately protected peptide having an activated ester group with an appropriately protected peptide having a free amino group; condensing ##STR2## by means of the azide method with ##STR3## followed by hydrogenolysis of the reaction product to obtain ##STR4## condensing the latter by means of the azide method with ##STR5## followed by treating the resulting compound with hydrazine hydrate to obtain ##STR6## condensing the latter by means of the azide method with ##STR7## in which R is hydrogen or CONHCH.sub.2 CONHCH.sub.2 CH.sub.3 to obtain the linear protected peptide ##STR8## in which R is as defined herein; thereafter said linear peptide is transformed into the desired cyclic peptide of formula 1 by deprotecting and oxidizing processes. In addition, the linear, reduced form of the peptide of formula 1a is obtained by deprotection of the aforementioned

linear peptide or by reduction of the cyclic peptide. The peptides of formulae 1 and 1a are useful for the management of diabetes and the treatment of acromegaly. Methods for their use are also disclosed.
TITLE: Derivatives of retro-enantio-**somatostatin**, intermediates therefor, and process therefor

SUMMARY:

BSUM(3)

This invention relates to derivatives of the tetradecapeptide **somatostatin**. More particularly, this invention concerns peptide derivatives of retro-enantio-**somatostatin** and salts thereof, a process for preparing the peptide derivatives and salts, intermediates used in the process and methods for. . .

SUMMARY:

BSUM(5)

The name "**somatostatin**" has been proposed for the factor found in hypothalamic extracts which inhibits the secretion of growth hormone (somatotropin). The structure. . .

SUMMARY:

BSUM(7)

The constitution of the tetradecapeptide **somatostatin** has been confirmed by synthesis; for example, see D. Sarantakis and W. A. McKinley, Biochem. Biophys. Res. Comm., 54, 234. . .

SUMMARY:

BSUM(9)

The linear form of **somatostatin**, having two sulfhydryl groups instead of a disulfide bridge, has been prepared recently by J.W.F. Rivier, J. Amer. Chem. Soc., 96, 2986 (1974). He reports that the linear form is equipotent to **somatostatin** based on the ability of the two compounds to inhibit the rate of secretion of growth hormone by rat pituitary. . .

SUMMARY:

BSUM(10)

Only recently have there been reported polypeptides, other than the natural hormone and its linear form, having **somatostatin**-like activity. D. Sarantakis, et al., Biochem. Biophys. Res. Comm., 55, 538 (1973) reported the synthesis of the **somatostatin** analog, [Ala.sup.3,14]-**somatostatin**, by solid phase methods. This analog exhibited a very small amount of activity, about 0.01% of **somatostatin**'s potency. P. Brazeau, et al., Biochem. Biophys. Res. Comm., 60, 1202 (1974) recently reported the synthesis of a number of acylated des[Ala.sup.1 -Gly.sup.2]-**somatostatin** compounds, by solid phase methods.

SUMMARY:

BSUM(11)

The present invention discloses new analogs of **somatostatin** based on the principle of the retro-enantio system. This system is achieved by construction of a reversed sequence of amino. . . instead of L, to give the "retro-enantio" isomer of the natural peptide. It is surprising that the retro-enantio derivatives of **somatostatin** of formulae I or Ia have been found to retain the activity of the natural hormone **somatostatin** notwithstanding the fact that other hormones of the retro-enantio system have shown a range of retention of full activity to. . .

SUMMARY:

BSUM(12)

The present invention discloses retro-enantio peptide derivatives which retain the activity of the natural hormone **somatostatin**. The derivatives are prepared readily by a convenient process, which includes the following advantages: the process starts from readily available. . .

SUMMARY:

BSUM(41)

The . . . as well as their corresponding pharmaceutically acceptable salts, are useful because they possess the pharmacological activity of the natural hormone **somatostatin**. Their activity is demonstrated readily in pharmacological tests such as a modification [A. V. Schally, et al., Biochem. Biophys. Res.. . .

SUMMARY:

BSUM(42)

The . . . test the peptides of this invention show a level of activity which is of the same order as that of **somatostatin**.

SUMMARY:

BSUM(66)

Finally, . . . G-25 and acetic acid is employed, the product is obtained in the form of its acetic acid addition salt. Repeated **lyophilization** from water of the product in the form of its **acetic** **acid** addition salt yields the substantialy pure cyclic **peptide** of formula I in which R is as defined herein, in the form of the free base.

DETDESC:

DETD(49)

A . . . phase of n-butanol-acetic acid-water (4:1:5) and then equilibrated in the upper phase) using the upper phase to desorb the cyclic **peptide**. The fractions containing the pure cyclic **peptide** are combined and **lyophilized** to give the title compound in the form of its **acetic** **acid** addition salt; .lambda..sub.max.sup.MeOH 290 (.epsilon. 5,415), 282 (.epsilon. 6,000) and 274 nm (.epsilon. 5,660). Repeated lyophilization of the latter compound. . .

US PAT NO: 3,929,758 [IMAGE AVAILABLE] L1: 43 of 45
DATE ISSUED: Dec. 30, 1975
TITLE: Cyclization of cysteine-containing peptides
INVENTOR: John Lawrence Hughes, Kankakee, Bourbonnais, IL
Jay Kenneth Seyler, Bourbonnais, IL
Robert Chung-Huang Liu, Kankakee, IL
ASSIGNEE: Armour Pharmaceutical Company, Phoenix, AZ (U.S. corp.)
APPL-NO: 05/505,344
DATE FILED: Sep. 12, 1974
ART-UNIT: 124
PRIM-EXMR: Lewis Gotts
ASST-EXMR: Reginald J. Suyat
LEGAL-REP: Richard R. Mybeck, Carl C. Batz

US PAT NO: 3,929,758 [IMAGE AVAILABLE] L1: 43 of 45

ABSTRACT:
The synthesis of a disulfide cyclic peptide by preparing peptide containing at least two cysteine moieties in its amino acid chain one of which is protected by an n-alkylthio group, and subjecting such peptide to a procedure in which the peptide is held in solution substantially free of oxygen at a pH of from about 5 to 10 until rearrangement takes place to yield a cyclic disulfide peptide and to displace said n-alkylthio group from said amino acid chain. The disclosure also embraces said non-cyclic peptides as new compounds and the processes by which they are perpared.

SUMMARY:

BSUM(4)

Many . . . the cysteine groups at positions 1 and 6 in their amino acid sequences (Handbook of Biochemistry, pages C-164 to C-188). **Somatostatin**, a recently discovered disulfide-containing peptide (P. Brazeau, et al, Science, 179, 77 [1973]), has been proposed to be of therapeutic value in the treatment of acromegaly and diabetes. **Somatostatin** contains a disulfide bond between the cysteine residues in positions 3 and 14 in its amino acid sequence (R. Burgus,. . .

SUMMARY:

BSUM(5)

Although the kind and sequence of the amino acid groups for the calcitonins, oxytocin, vasopressin, **somatostatin** and other such naturally occurring peptides may vary depending upon the species from which they are obtained, all such peptides. . .

SUMMARY:

BSUM(6)

TABLE I

Typical Peptides Containing
Cysteine Ring Structures
Oxytocin:
H--CYS--TYR--ILE--GLN--ASN--CYS--PRO--LEU--GLY--NH.sub.2
Vasopressin:
H--CYS--TYR--PHE--GLN--ASN--CYS--PRO--ARG--GLY--NH.sub.2
Somatostatin:
H--ALA--GLY--CYS--LYS--ASN--PHE--PHE--TRP--LYS--THR
PHE--THR--SER--CYS
.vertline.
OH
Salmon H--CYS--SER--ASN--LEU--SER--THR--CYS--VAL--LEU--GLY
Calcitonin:
LYS--LEU--SER--GLN--GLU--LEU--HIS--LYS--LEU--GLN--THR
TYR--PRO--ARG--THR--ASN--THR--GLY--SER--GLY--THR--PRO--NH.sub.2
Human H--CYS--GLY--ASN--LEU--SER--THR--CYS--MET--LEU--GLY
Calcitonin:
THR--TYR--THR--GLN--ASP--PHE--ASN--LYS--PHE--HIS. . .

SUMMARY:

BSUM(26)

In . . . groups at the 6th and 1st positions may be reversed. As to Table VI which refers to the synthesis of **somatostatin**, we prefer to place the n-alkylthio group at the 14th position and a BZ group at the 3rd position as. . .

DETDESC:

DETD(70)

The . . . portions of ethyl acetate. The peptide was extracted from the resin beads with 2 .times. 50 ml portions of glacial **acetic** **acid**. The extract was **lyophilized** to 486 mg of cleaved **peptide**.

DETDESC:

DETD(76)

Our improved process may also be applied in a similar manner to the synthesis of **somatostatin**. The resin may be the polystyrene resin such as the chloromethylated polystyrene resin known to the art. Cysteine, at position. . .

DETDESC:

DETD(181)

The . . . ml portions of ethyl acetate. The peptide was extracted from the resin beads with 2 .times. 50 ml of glacial **acetic** **acid**. The extract was **lyophilized** to give 1063 mg of cleaved **peptide**.

DETDESC:

DETD(190)

To apply our improved process in the synthesis of **somatostatin**, the amino acid chain for **somatostatin** may be built using the reactants set forth in Table VI or equivalents thereof. The formula of the peptide resulting. . .

DETDESC:

DETD(192)

After subjecting this peptide to our improved cyclizing method as herein described, the peptide becomes: ##EQU21## which is **somatostatin**.

CLAIMS:

CLMS(33)

33. A peptide as set forth in claim 27 in which said amino acid chain is the same as in **somatostatin**.

US PAT NO: 3,904,594 [IMAGE AVAILABLE] L1: 44 of 45
DATE ISSUED: Sep. 9, 1975
TITLE: **Somatostatin** and acylated des-(ala.sup.1, gly.sup.2) derivatives thereof
INVENTOR: Roger C. L. Guillemin, La Jolla, CA
Paul E. Brazeau, Jr., Solana Beach, CA
Roger C. Burgus, Leucadia, CA
Nicholas C. Ling, San Diego, CA
Jean E. F. Rivier, La Jolla, CA
Wylie W. Vale, Jr., La Jolla, CA
ASSIGNEE: The Salk Institute for Biological Studies, San Diego, CA (U.S. corp.)
APPL-NO: 05/478,175
DATE FILED: Jun. 12, 1974
ART-UNIT: 124
PRIM-EXMR: Lewis Gotts
ASST-EXMR: Reginald J. Suyat
LEGAL-REP: Fitch, Even, Tabin & Luedeka

US PAT NO: 3,904,594 [IMAGE AVAILABLE] L1: 44 of 45

ABSTRACT:
Various peptides have been prepared which inhibit the secretion of growth hormone in mammalians, including humans. The peptides are useful in the treatment of acromegaly and diabetes and are also useful in controlling the release of thyroid stimulating hormone.
TITLE: **Somatostatin** and acylated des-(ala.sup.1, gly.sup.2) derivatives thereof

SUMMARY:

BSUM(3)

The . . . ease of discussion herein, a material exhibiting inhibitory effect on the secretion of growth hormone (somatotropin) is referred to as "**somatostatin**." The particular peptides of the present invention which have been found effective to inhibit the secretion of growth hormone are sometimes referred to herein as **somatostatin** peptides.

SUMMARY:

BSUM(6)

FIGS. . . . and 2b show the rate of human growth hormone secretion in the subject after administration of growth hormone stimulants and **somatostatin**.

SUMMARY:

BSUM(7)

Generally, . . . The aqueous phase from the second extraction was subjected to ion-exchange chromotography on carboxymethyl cellulose. This provided a fraction with **somatostatin** activity. This fraction was further purified by gel filtration on "Sephadex G-25" gel in 0.5 molar acetic acid. Further purification. . .

SUMMARY:

BSUM(14)

R . . . (Tyr) may be substituted for any Phe. It is also likely that any of the amino acid moieties in the **somatostatin** peptide can be substituted by other amino acids.

SUMMARY:

BSUM(19)

Each of the amino acids in that portion of the **somatostatin** peptides of the present invention extending between and including the two Cys groups, are the L-isomer composed the amino acid. . .

SUMMARY:

BSUM(20)

The **somatostatin** peptides of the present invention were synthesized by solid phase techniques. The synthesis was conducted in a stepwise manner on. . . 0.5 to 2 millimoles of chlorine per gram of resin. Herein below, in the further description of the synthesis of **somatostatin** peptides, the reagents used will be first listed by their chemical name and their common abbreviation in parenthesis. Thereafter, the. . .

SUMMARY:

BSUM(22)

After . . . in accordance with the following schedule: Schedule for coupling of amino acids other than Asn in solid phase synthesis of **Somatostatin**

SUMMARY:

BSUM(25)

The above schedule was used for coupling of each of the amino acids of the **somatostatin** peptide to Cys with the exception of Asn. For Asn, steps 1 through 8 are the same and the following. . .

SUMMARY:

BSUM(26)

Schedule for Boc-Asn-ONp coupling in solid phase synthesis of **Somatostatin**

Step	Reagents and operations	Mix times min.
9	DMF wash 60 ml (3 times)	3
10.	. .	

SUMMARY:

BSUM(29)

Cleavage . . . performed in hydrofluoric acid in the presence of 100 molar anisole. After elemination of hydrofluoric acid under high vacuum, the **peptide** was washed with ether and extracted with degassed dilute **acetic** **acid**. **Lyophilization** of the acetic acid extract provided a white fluffy material. This material was subjected to gel filtration in 2N acetic. . .

SUMMARY:

BSUM(30)

Active . . . can be used in solid phase synthesis and the classical method of synthesis can also be used to prepare the **somatostatin** peptides of the invention.

SUMMARY:

BSUM(31)

An in vitro assay of the effectiveness of **somatostatin** peptides has been devised. The assay is made by treating pituitary glands removed from rats to separate cells therefrom. The. . . prior to use in the assay. Following media changes, cell cultures incubated for a period of 4 hours and particular **somatostatin** peptides are added thereto. Radioimmunoassay analysis is used to determine the rate of growth hormone secretion which is expressed in nanograms per hour. The results for

various **somatostatin** materials are reported herein below in TABLE 1.

SUMMARY:

BSUM(33)

Effects of ovine hypothalamic extracts and **somatostatin** peptides on the secretion of growth hormone by rat pituitary cells in monolayer cultures; N. number of cell culture dishes;. . .

SUMMARY:

BSUM(34)

Somatostatin Material	Level of Use	N	rGH (ng/hr)
Control (no somatostatin material)		4	421.7 .+-. 49.1
Hypothalamic extract. . . extract	0.1 fragment/ml	3	120.0 .+-. 22.7
Hypothalamic extract	0.5 fragment/ml	3	50.7 .+-. 16.4
Bridged **somatostatin** peptide where R is H-Ala-Gly	0.2nM	3	304.0 .+-. 45.5
H-Ala-Gly	1.0nM	3	210.7 .+-. 17.0
H-Ala-Gly	5.0nM	3	70.7 .+-. 16.8
H-Ala-Gly	25.0nM	4	52.5 .+-. 2.4
Linear **somatostatin** peptide where R is H-Ala-Gly	0.2nM	3	420.0 .+-. 23.1
H-Ala-Gly	1.0nM	4	205.0 .+-. 23.8
H-Ala-Gly	5.0nM	3. . .	

SUMMARY:

BSUM(35)

The . . . weight ratio of 100:810:5:90. The level of use of hypothalamic extract is based on a unit which corresponds to the **somatostatin** material which can potentially be extracted from a single hypothalamic fragment.

SUMMARY:

BSUM(36)

The results indicate consistent inhibition of the secretion of growth hormone of the pituitary monolayer cultures by the **somatostatin** materials described in Table 1.

SUMMARY:

BSUM(37)

A synthetically produced linear **somatostatin** peptide was used to test the effectiveness of the peptide in inhibiting the secretion of growth hormone in rats. The **somatostatin** peptide had the following structure:

SUMMARY:

BSUM(39)
To . . . third day 9 rats were injected with 0.5ml. of saline and 36 rats were injected with various levels of the **somatostatin** peptide. Fifteen minutes after the injection the rats were decapitated and blood samples were taken. The blood samples were assayed. . .

SUMMARY:

BSUM(40)
. . .
2

Injection	Number of Rats	GH/ml Serum in Nanograms/ml
Saline	9	91.6 .+-. 10.2
0.4 .mu.g **Somatostatin** peptide	9	57.9 .+-. 8.9
2.0 .mu.g **Somatostatin** peptide	9	38.6 .+-. 7.3
10.0 .mu.g **Somatostatin** peptide	9	15.9 .+-. 2.9
50.0 .mu.g **Somatostatin** peptide	9	12.9 .+-. 3.6

SUMMARY:

BSUM(41)

A synthetically produced **somatostatin** peptide corresponding to the following structure was used to test the effectiveness of the peptide in humans:

SUMMARY:

BSUM(43)

Since . . . administered or arginine was started to be infused into the subject. Also, starting at time 0, 250 micrograms of the **somatostatin** peptide was injected intravenously into the subject. A further amount of the **somatostatin** peptide was infused uniformly over a period of 30 minutes or 1 hour to the subject starting at the time. .

SUMMARY:

BSUM(44)

TABLE 3

Subject No.	Growth Hormone Stimulant	Level of Use of Growth Hormone Stimulant	Amount of Peptide Injected Intravenously at Time 0	Amount of **Somatostatin** Infused
1	L-Dopa	0.5 g	250 .mu.g	500 .mu.g. . .

SUMMARY:

BSUM(45)

The . . . L-Dopa and arginine respectively; this constitutes a control. The inhibiting effect on the rate of growth hormone secretion by the **somatostatin** peptide is shown in the graphs of FIGS. 1b and 2b for L-Dopa and arginine respectively. The graphs show the. . .

SUMMARY:

BSUM(46)

The clinical significance of **somatostatin** peptides of the present invention are readily apparent for the treatment of any abnormality involving an increased level of secretion of growth hormone. Particularly, the **somatostatin** peptides of the present invention are considered to be useful in the treatment of acromegaly and in the management of diabetes; in the latter case this would be implemented either by administration of **somatostatin** alone or in conjunction with insulin. The **somatostatin** peptides of the present invention have also been found effective to inhibit the secretion of thyroid stimulating hormone by the. . .

SUMMARY:

BSUM(47)

The ability of the **somatostatin** peptides of the present invention to inhibit TSH secretion are illustrated by the following experiment. It is known that a. . . In a series of experiments, anesthetized rats were injected with various levels of TRF and TRF in combination with a **somatostatin** peptide of the present invention. The **somatostatin**

peptide had the following structure:

SUMMARY:

BSUM(50)

. . .

TRF 5 3.615 .+-. 0.223
4 120 ng TRF 5 6.215 .+-. 0.919
5 120 ng TRF + 300 ng **somatostatin** peptide
5 5.168 .+-. 0.462
6 120 ng TRF + 1 .mu.g **somatostatin** peptide
5 4.128 .+-. 0.741
7 120 ng TRF + 10 .mu.g **somatostatin** peptide
5 2.054 .+-. 0.304
Multiple Range Test of Duncan: 4 vs 5 < .05; 4 vs 6 >. . .

SUMMARY:

BSUM(51)

It is anticipated that various modifications may be made in the **somatostatin** peptides of the present invention. Such modifications in the peptide structure are considered within the spirit and scope of the.
. .

US PAT NO: 3,863,008 [IMAGE AVAILABLE] L1: 45 of 45
DATE ISSUED: Jan. 28, 1975
TITLE: **SOMATOSTATIN** AS STIMULANT OF LUTEINIZING HORMONE SECRETION
INVENTOR: Norman H. Grant, Wynnewood, PA
ASSIGNEE: American Home Products Corporation, New York, NY (U.S. corp.)
APPL-NO: 05/368,557
DATE FILED: Jun. 11, 1973
ART-UNIT: 124
PRIM-EXMR: Lewis Gotts
ASST-EXMR: Reginald J. Suyat

US PAT NO: 3,863,008 [IMAGE AVAILABLE] L1: 45 of 45

ABSTRACT:
Somatostatin and its linear counterpart are described as stimulating the release of luteinizing hormone.
TITLE: **SOMATOSTATIN** AS STIMULANT OF LUTEINIZING HORMONE SECRETION

ABSTRACT:
Somatostatin and its linear counterpart are described as stimulating the release of luteinizing hormone.

SUMMARY:

BSUM(1)

This invention relates to the tetradecapeptide **somatostatin** and its linear counterpart and the use of these tetradecapeptides in stimulating

the release of luteinizing hormone and hence promoting. . .

SUMMARY:

BSUM(2)

Somatostatin is the tetradecapeptide H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH. This tetradecapeptide has only recently been identified by isolation from extracts of ovine hypothalamic tissues and. . . al., supra, to have been synthesized by solid phase methodology and found to have the same biological activity as the **somatostatin** obtained from a natural source. In addition the solid phase synthesis of H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH, the linear form of **somatostatin**, has been reported.

SUMMARY:

BSUM(3)

The present invention relates to the discovery that **somatostatin** and its linear counterpart are useful in stimulating the release of luteinizing hormone. Luteinizing hormone is one of the hormones. . .

SUMMARY:

BSUM(4)

As used herein **somatostatin** means the tetradecapeptide of the formula

SUMMARY:

BSUM(6)
whether obtained from natural sources or made synthetically. It also includes those materials of natural origin which contain **somatostatin** in non-isolated form such as extract of ovine hypothalamic tissue. The linear counterpart of **somatostatin** embraced by the present invention is represented by the formula H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH. Thus, the structural difference between **somatostatin** and its linear counterpart is that the former has a bridging bond between the sulfhydryls of the two cysteinyl amino acid residues in the tetradecapeptide. The definition of **somatostatin** and the linear counterpart of **somatostatin** also includes those compounds having a side chain protecting group on an amino acid residue of such tetradecapeptide. Thus, for. . .

SUMMARY:

BSUM(8)

Also included within the scope of the present invention are non-toxic acid addition salts of **somatostatin** and its linear counterpart such as hydrochloride, hydrobromide, sulfate, phosphate, maleate, acetate, citrate, benzoate, succinate, malate, ascorbate, and the like.

DETDESC:

DETD(1)

The following examples are illustrative of the preparation of **somatostatin** and its linear counterpart.

DETDESC:

DETD(11)
Somatostatin

DETDESC:

DETD(19)
Di-S-carboxymethyl **Somatostatin**

DETDESC:

DETD(20)

To . . . acetate buffer (pH 8.5). The mixture is incubated for 4.5 hours at room temperature, after which 20 .mu.l of glacial **acetic** **acid** is added and the solution is **lyophilized**. To the reduced **peptide** in 800 .mu.l of 0.5M pyridine acetate--0.005M 2-mercaptoethanol buffer (pH 6.0) is added 200 .mu.l of 0.1M iodoacetic acid in. . .

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=> s lyophil?(15a)transfer?(3a)water(15a)peptide
         19118 LYOPHIL?
        498926 TRANSFER?
        651081 WATER
         17043 PEPTIDE
L1           3 LYOPHIL?(15A)TRANSFER?(3A)WATER(15A)PEPTIDE

=> d bib ab kwic 1-


US PAT NO:      4,908,475 [IMAGE AVAILABLE]            L1: 1 of 3
DATE ISSUED:    Mar. 13, 1990
TITLE:          Intermediates for preparing 1,6-dicarba-vasopressin
                  compounds
INVENTOR:       James F. Callahan, Philadelphia, PA
                William F. Huffman, Malvern, PA
                Kenneth A. Newlander, West Chester, PA
                Nelson C. F. Yim, Ambler, PA
ASSIGNEE:       SmithKline Beckman Corporation, Philadelphia, PA (U.S.
                  corp.)
APPL-NO:        07/192,736
DATE FILED:     May 9, 1988
ART-UNIT:       126
PRIM-EXMR:      Michael L. Shippen
LEGAL-REP:      Charles M. Kinzig, Janice E. Williams, Alan D. Lourie

US PAT NO:      4,908,475 [IMAGE AVAILABLE]            L1: 1 of 3

ABSTRACT:
New compounds which have potent V.sub.2 -vasopressin antagonistic
activity are prepared by a 1,6-cyclization using peptide bond formation.
The structures of the compounds are characterized by a Pas.sup.1,6 or
Tas.sup.1,6 cyclized unit. Also a chiral synthesis of the optically pure
Pas intermediates is described.

DETDESC:

DETD(45)

 This crude **peptide** was purified by counter current distribution
```

(CCD) in BAW (butanol/acetic acid/**water**) 4:1:5 in 240 **transfers**. Fractions were checked by tlc and appropriate fractions were pooled, evaporated under reduced pressure and **lyophilized** from 1% aqueous acetic acid to yield:

US PAT NO: 4,810,778 [IMAGE AVAILABLE] L1: 2 of 3
DATE ISSUED: Mar. 7, 1989
TITLE: Intermediates for preparing 1,6-dicarba-vasopressin compounds
INVENTOR: James F. Callahan, Philadelphia, PA
William F. Huffman, Malvern, PA
Kenneth A. Newlander, West Chester, PA
Nelson C. F. Yim, Ambler, PA
ASSIGNEE: SmithKline Beckman Corporation, Philadelphia, PA (U.S. corp.)
APPL-NO: 07/191,673
DATE FILED: May 9, 1988
ART-UNIT: 186
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Janice E. Williams, Stuart R. Suter, Alan D. Lourie

US PAT NO: 4,810,778 [IMAGE AVAILABLE] L1: 2 of 3

ABSTRACT:
New compounds which have potent V.sub.2 -vasopressin antagonistic activity are prepared by a 1,6-cyclization using peptide bond formation. The structures of the compounds are characterized by the Pas.sup.1,6 or Tas.sup.1,6 cyclized unit. Also a chiral synthesis of the optically pure Pas intermediates is described.

DETDESC:

DETD(45)

This crude **peptide** was purified by counter current distribution (CCD) in BAW (butanol/acetic acid/**water**) 4:1:5 in 240 **transfers**. Fractions were checked by tlc and appropriate fractions were pooled, evaporated under reduced pressure and **lyophilized** from 1% agueous acetic acid to yield:

US PAT NO: 4,760,052 [IMAGE AVAILABLE] L1: 3 of 3
DATE ISSUED: Jul. 26, 1988
TITLE: 1,6-dicarba-vasopressin compounds
INVENTOR: James F. Callahan, Philadelphia, PA
William F. Huffman, Malvern, PA
Kenneth A. Newlander, West Chester, PA
Nelson C. F. Yim, Ambler, PA
ASSIGNEE: Smithkline Beckman Corporation, Philadelphia, PA (U.S. corp.)
APPL-NO: 07/043,658
DATE FILED: Apr. 28, 1987
ART-UNIT: 153
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Janice E. Williams, Stuart R. Suter, Alan D. Lourier

US PAT NO: 4,760,052 [IMAGE AVAILABLE] L1: 3 of 3

ABSTRACT:
New compounds which have potent V.sub.2 -vasopressin antagonistic activity are prepared by a 1,6-cyclization using peptide bond formation. The structures of the compounds are characterized by a Pas.sup.1,6 or Tas.sup.1,6 cyclized unit. Also a chiral synthesis of the optically pure Pas intermediates is described.

DETDESC:

DETD(46)

This crude **peptide** was purified by counter current distribution (CCD) in BAW (butanol/acetic acid/**water**) 4:1:5 in 240 **transfers**. Fractions were checked by tlc and appropriate fractions were pooled, evaporated under reduced pressure and **lyophilized** from 1% aqueous acetic acid to yield:

=>
=> s lyophil?(15a)dilut?(3a)water(15a)peptide
19118 LYOPHIL?
192361 DILUT?
651081 WATER
17043 PEPTIDE
L2 43 LYOPHIL?(15A)DILUT?(3A)WATER(15A)PEPTIDE

=> s l2 and py<1993
1648598 PY<1993
L3 27 L2 AND PY<1993

=> d kwic 1-

US PAT NO: 5,157,019 [IMAGE AVAILABLE] L3: 1 of 27
DATE ISSUED: **Oct. 20, 1992**

DETDESC:

DETD(44)

Upon . . . mixed with the 40 ml acetic acid aliquot for about 5 minutes before filtering. The filtrate containing the dissolved subject **peptide** is then **diluted** 1:2 (v/v) with distilled **water** and **lyophilized**.

US PAT NO: 4,908,475 [IMAGE AVAILABLE] L3: 2 of 27
DATE ISSUED: **Mar. 13, 1990**

DETDESC:

DETD(55)

The . . . then extracted with 10% HOAc (120 ml), 1% HOAc (120 ml) and water (120 ml). The aqueous extracts were combined, **diluted** with **water** and **lyophilized** to yield 213 mg crude linear **peptide**. 100 mg crude linear **peptide** was purified by gel filtration on G-15 with 1% HOAc to yield 62 mg purified linear peptide.

DETDESC:

DETD(67)

The . . . was then extracted with 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 324 mg crude linear **peptide**. 275 mg linear **peptide** was purified by countercurrent distribution (nBuOH/HOAc/water 4:1:5) to yield 166.7 mg purified linear peptide.

DETDESC:

DETD(74)

The . . . was then extracted with 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 335 mg crude linear **peptide**. The crude linear **peptide** was purified by countercurrent distribution (nBuOH/HOAc/water 4:1:5) to yield 287.9 mg partially purified linear peptide. 100 mg of the partially. . .

DETDESC:

DETD(77)

The . . . 30 ml 50% HOAc, 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 564 mg crude linear **peptide**. The resin was re extracted with DMF, which was evaporated to dryness and the residue lyophilized from 10% HOAc to. . .

US PAT NO: 4,826,813 [IMAGE AVAILABLE] L3: 3 of 27
DATE ISSUED: **May 2, 1989**

DETDESC:

DETD(58)

The appropriate fractions are combined and concentrated. The residue is dissolved in conc. acetic acid, **diluted** with **water** and **lyophilized** to give the title **peptide** which is used without further purification for the synthesis of the tail modified peptides.

US PAT NO: 4,810,778 [IMAGE AVAILABLE] L3: 4 of 27
DATE ISSUED: **Mar. 7, 1989**

DETDESC:

DETD(62)

The . . . then extracted with 10% HOAc 120 ml), 1% HOAc (120 ml) and water (120 ml). The aqueous extracts were combined, **diluted** with **water** and **lyophilized** to yield 213 mg crude linear **peptide**. 100 mg crude linear **peptide** was purified by gel filtration on G-15 with 1% HOAc to yield 62 mg purified linear peptide.

DETDESC:

DETD(75)

The . . . was then extracted with 60 ml 10% HOAc. 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 324 mg crude linear **peptide**. 275 mg linear **peptide** was purified by countercurrent distribution (nBuOH/HOAc/water 4:1:5) to yield 166.7 mg purified linear peptide.

DETDESC:

DETD(82)

The . . . was then extracted with 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 335 mg crude linear **peptide**. The crude linear **peptide** was purified by countercurrent distribution (nBuOH/HOAc/water 4:1:5) to yield 287.9 mg partially purified linear peptide. 100 mg of the partially. . .

DETDESC:

DETD(85)

The . . . 30 ml 50% HOAc, 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 564 mg crude linear **peptide**. The resin gas re-extracted with DMF, which was evaporated to dryness and the residue lyophilized from 10% HOAc to yield. . .

US PAT NO: 4,760,052 [IMAGE AVAILABLE] L3: 5 of 27
DATE ISSUED: **Jul. 26, 1988**

DETDESC:

DETD(56)

The . . . then extracted with 10% HOAc (120 ml), 1% HOAc (120 ml) and water (120 ml). The aqueous extracts were combined, **diluted** with **water** and **lyophilized** to yield 213 mg crude linear **peptide**. 100 mg crude linear **peptide** was purified by gel filtration on G-15 with 1% HOAc to yield 62 mg purified linear peptide.

DETDESC:

DETD(69)

The . . . was then extracted with 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 324 mg crude linear **peptide**. 275 mg linear **peptide** was purified by countercurrent distribution (nBuOH/HOAc/water 4:1:5) to yield 166.7 mg purified linear peptide.

DETDESC:

DETD(76)

The . . . was then extracted with 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 335 mg crude linear **peptide**. The crude linear **peptide** was purified by countercurrent distribution (nBuOH/HOAc/water 4:1:5) to yield 287.9 mg partially purified linear peptide. 100 mg of the partially. . .

DETDESC:

DETD(79)

The . . . 30 ml 50% HOAc, 60 ml 10% HOAc, 60 ml 1% HOAc and 60 ml water. The extracts were combined, **diluted** with **water** and **lyophilized** to yield 564 mg crude linear **peptide**. The resin was re extracted with DMF, which was evaporated to dryness and the residue lyophilized from 10% HOAc to. . .

US PAT NO: 4,711,877 [IMAGE AVAILABLE] L3: 6 of 27
DATE ISSUED: **Dec. 8, 1987**

DETDESC:

DETD(38)

Product containing fractions (TLC) are combined and concentrated. The residue is dissolved in conc. acetic acid, **diluted** with **water** and **lyophilized** to yield the acid **peptide**.

US PAT NO: 4,705,778 [IMAGE AVAILABLE] L3: 7 of 27
DATE ISSUED: **Nov. 10, 1987**

DETDESC:

DETD(15)

After . . . the reaction HF was completely evaporated under vacuum. The resin was washed with anhydrous ether 3.times. to remove anisole. The **peptide** was extracted into 50% acetic acid (25 mL). The extract was **diluted** with **water** and **lyophilized**. Crude **peptide** was subjected to gel filtration on Sephadex G-15 (2.5.times.83 cm) using 40% acetic acid as eluent. Peptide was then purified. . .

US PAT NO: 4,684,622 [IMAGE AVAILABLE] L3: 8 of 27
DATE ISSUED: **Aug. 4, 1987**

DETDESC:

DETD(129)

Product containing fractions (TLC) are combined and concentrated. The residue is dissolved in conc. acetic acid, **diluted** with **water** and **lyophilized** to yield the acid **peptide**. The Cys(OH) or Z(OH) intermediates are used, without further purification, for the synthesis of the end product peptides.

US PAT NO: 4,643,988 [IMAGE AVAILABLE] L3: 9 of 27

DATE ISSUED: **Feb. 17, 1987**

DETDESC:

DETD(23)

Release . . . h. The reaction mixture was diluted with ether (500 ml) and filtered. The residue was washed with 50% acetic acid, **diluted** with **water** and **lyophilized** to obtain 230 mg of the **peptide**. This was then treated with 0.1M hydroxylamine hydrochloride solution (pH 9.5 100 ml) for 15 h. The pH was adjusted. . .

US PAT NO: 4,626,524 [IMAGE AVAILABLE] L3: 10 of 27
DATE ISSUED: **Dec. 2, 1986**

DETDESC:

DETD(36)

Peptides . . . pp. 51-85, Dekker, N.Y.). After drying the resin in vacuo, the residual anisole was extracted by diethyl ether, and the **peptide** was extracted from the resin by glacial acetic acid. The peptides were recovered by **lyophilization** of the glacial acetic acid **diluted** with distilled **water** (1:10, v/v). The N-terminus of the pentapeptides was blocked with benzyloxycarbonyl (Cbz) Bergmann, M. and Zervas, L. (1932) Ber. Dtsch.. . .

US PAT NO: 4,624,943 [IMAGE AVAILABLE] L3: 11 of 27
DATE ISSUED: **Nov. 25, 1986**

DETDESC:

DETD(4)

1.1 . . . trifluoroacetic acid) in 20 ml fractions. Fractions 11-17 were combined and concentrated. The residue was dissolved in conc. acetic acid, **diluted** with **water** and **lyophillized** to yield 189 mg of the D-Tyr(Et).sup.2 -Pro.sup.7 **peptide**, which was used without further purification for the synthesis of the tail modified peptides. The D-Tyr.sup.2 congener was prepared similarly.

US PAT NO: 4,599,324 [IMAGE AVAILABLE] L3: 12 of 27
DATE ISSUED: **Jul. 8, 1986**

DETDESC:

DETD(126)

Product containing fractions (TLC) are combined and concentrated. The residue is dissolved in conc. acetic acid, **diluted** with **water** and **lyophilized** to yield the acid **peptide**. The Cys(OH) or Z(OH) intermediates are used, without further purification, for the synthesis of the end product peptides.

US PAT NO: 4,587,045 [IMAGE AVAILABLE] L3: 13 of 27
DATE ISSUED: **May 6, 1986**

DETDESC:

DETD(107)

Fractions 11-17 were combined and concentrated. The residue was dissolved in conc. acetic acid, **diluted** with **water** and **lyophilized** to yield 189 mg of the D-Tyr(Et).sup.2, proline **peptide**, which was used without further purification for the synthesis of the tail modified peptides.

DETDESC:

DETD(113)

The . . . water). The eluant was evaporated to dryness. The residue was dissolved in a small amount of 10% acetic acid and **diluted** with **water** to 1% acetic acid, then **lyophilized**, yielding 650 mg of the crude titled **peptide**.

US PAT NO: 4,560,505 [IMAGE AVAILABLE] L3: 14 of 27
DATE ISSUED: **Dec. 24, 1985**

DETDESC:

DETD(10)

After . . . the Pauly reaction indicated complete removal of the histadine protector group. The mixture was then centrifuged and the solution was **lyophilised** several times after **diluting** with **water**. The crude **peptide** was chromatographed at pH 7.0 on a column of carboxymethylcellulose (CM-52) eluting with a linear gradient of ammonium acetate in. . .

US PAT NO: 4,543,349 [IMAGE AVAILABLE] L3: 15 of 27
DATE ISSUED: **Sep. 24, 1985**

DETDESC:

DETD(7)

Fractions 11-17 were combined and concentrated. The residue was dissolved in conc. acetic acid, **diluted** with **water** and **lyophillized** to yield 189 mg of the D-Tyr(Et).sup.2 -Pro.sup.7 **peptide**, which was used without further purification for the synthesis of the tail modified peptides.

US PAT NO: 4,542,124 [IMAGE AVAILABLE] L3: 16 of 27
DATE ISSUED: **Sep. 17, 1985**

DETDESC:

DETD(114)

Fractions 11-17 were combined and concentrated. The residue was dissolved in conc. acetic acid, **diluted** with **water** and **lyophillized** to yield 189 mg of the D-Tyr(Et).sup.2, proline **peptide**, which was used without further purification for the

synthesis of the tail modified peptides.

DETDESC:

DETD(121)

The . . . water). The eluant was evaporated to dryness. The residue was dissolved in a small amount of 10% acetic acid and **diluted** with **water** to 1% acetic acid, then **lyophilized**, yielding 650 mg of the crude titled **peptide**.

US PAT NO: 4,444,682 [IMAGE AVAILABLE] L3: 17 of 27
DATE ISSUED: **Apr. 24, 1984**

DETDESC:

DETD(33)

Hexagastrin . . . MES for 45 minutes at 0.degree. C., dissolved in acetic acid and filtered to eliminate the resin. The solution is **diluted** with **water** and **lyophilized**, yielding 1.0 g of hexagastrin. 350 mg of this **peptide** is dissolved in 4 ml of DMF and 2 ml of pyridine, and 400 mg (1.8 mmoles) of acetylsulfuric acid. . .

US PAT NO: 4,427,660 [IMAGE AVAILABLE] L3: 18 of 27
DATE ISSUED: **Jan. 24, 1984**

DETDESC:

DETD(30)

The . . . the ice bath and allowed to come to room temperature. After 4 hours at room temperature, the whole solution is **diluted** with 20-fold excess of **water**, the solution is **lyophilized**, and volatile matter removed, leaving the formylated **peptide**. The formylated **peptide** is purified by dissolving it in water, bringing the pH to 5, and then passing the mixture over Dowex 50. . .

US PAT NO: 4,372,884 [IMAGE AVAILABLE] L3: 19 of 27
DATE ISSUED: **Feb. 8, 1983**

SUMMARY:

BSUM(19)

The . . . Bio Rex- 70 resin column with pyridine:acetic acid:water (30:4:66) or 50% acetic acid. Fractions were collected; only the ones containing **peptide** (ninhydrin positive) were **diluted** with **water** and immediately **lyophilized**. 1.2 g of crude cream colored material was obtained. It was applied onto a Sephadex G-25 F gel column (3.times.200. . .

US PAT NO: RE 30,548 [IMAGE AVAILABLE] L3: 20 of 27
DATE ISSUED: **Mar. 17, 1981**

DETDESC:

DETD(14)

The . . . Bio Rex-70 resin column with pyridine; acetic acid:water (30:4:66) or 50% acetic acid. Fractions were collected; only the ones containing **peptide** (ninhydrin positive) were **diluted** with **water** and immediately **lyophilized**. 950 mg of crude cream colored material was obtained. It was applied onto a Sephadex G-25 F gel column (3.times.200. . .

US PAT NO: 4,211,693 [IMAGE AVAILABLE] L3: 21 of 27
DATE ISSUED: **Jul. 8, 1980**

DETDESC:

DETD(16)

The . . . Bio Rex-70 resin column with pyridine: acetic acid:water (30:4:66) or 50% acetic acid. Fractions were collected; only the ones containing **peptide** (ninhydrin positive) were **diluted** with **water** and immediately **lyophilized**. 1.2 g of crude cream colored material was obtained. The material was applied onto a Sephadex G-25 F gel column. . .

US PAT NO: 4,148,787 [IMAGE AVAILABLE] L3: 22 of 27
DATE ISSUED: **Apr. 10, 1979**

DETDESC:

DETD(77)

200 . . . been equilibrated with 50% acetic acid. The flow rate was 100 ml/h. The peak, centered at 240 ml, was collected, **diluted** with **water** and **lyophilized** to give 87 mg of desalted **peptide** 12.

DETDESC:

DETD(102)

a . . . at a flow rate of 100 ml/h. The major peak detected at 280 nm, centered at 220 ml, was collected, **diluted** with one volume of **water** and **lyophilized** to give 90 mg. The desalted **peptide** was dissolved in 10 ml 0.2 M acetic acid, applied to a 2.5 .times. 105.0 cm Sephadex G-15 column, which. . .

DETDESC:

DETD(120)

a . . . at a flow rate of 100 ml/h. The major peak, detected at 280 nm, centered at 245 ml, was collected, **diluted** with one volume of **water** and **lyophilized** to give 54 mg. The desalted **peptide** (54 mg) was dissolved in 10 ml 0.2 M acetic acid, applied to a 2.5.times. 105.0 cm Sephadex G-15 column. . .

US PAT NO: 4,133,782 [IMAGE AVAILABLE] L3: 23 of 27
DATE ISSUED: **Jan. 9, 1979**

DETDESC:

DETD(15)

The . . . Bio Rex- 70 resin column with pyridine:acetic acid:water (30:4:66) or 50% acetic acid. Fractions were collected; only the ones containing **peptide** (ninhydrin positive) were **diluted** with **water** and immediately **lyophilized**. 1.2 g of crude cream colored material was obtained. It was applied onto a Sephadex G-25 F gel column (3. . .

US PAT NO: 4,105,603 [IMAGE AVAILABLE] L3: 24 of 27
DATE ISSUED: **Aug. 8, 1978**

DETDESC:

DETD(13)

The . . . Bio Rex-70 resin column with pyridine; acetic acid:water (30:4:66) or 50% acetic acid. Fractions were collected; only the ones containing **peptide** (ninhydrin positive) were **diluted** with **water** and immediately **lyophilized**. 950 mg of crude cream colored material was obtained. It was applied onto a Sephadex G-25 F gel column (3. . .

US PAT NO: 4,083,967 [IMAGE AVAILABLE] L3: 25 of 27
DATE ISSUED: **Apr. 11, 1978**

DETDESC:

DETD(87)

The . . . (6 ml) and water (3 ml) in the presence of 0.5 g 10% palladium on charcoal catalyst. The crude deprotected **peptide** was dissolved in 50 ml and 2% acetic acid, filtered to remove some dicyclohexylurea and **diluted** to 100 ml with **water** before **lyophilisation**. The product was then purified on a column of carboxymethylcellulose, eluting with gradients of ammonium acetate, pH 5.1. The peptide. . .

US PAT NO: 3,929,756 [IMAGE AVAILABLE] L3: 26 of 27
DATE ISSUED: **Dec. 30, 1975**

DETDESC:

DETD(16)

Amino . . . performed as described, the dried sample being oxidized for 12 hours at 0.degree.C. with 0.25 mls of performic acid reagent, **diluted** with cold **water**, **lyophilized** and acid hydrolyzed for amino acid analysis. Spectral analyses of the pure **peptide** were performed on a Cary model 15 recording spectrophotometer to quantitate tyrosine and tryptophan content.

US PAT NO: 3,912,711 [IMAGE AVAILABLE] L3: 27 of 27
DATE ISSUED: **Oct. 14, 1975**

DRAWING DESC:

DRWD(32)

A . . . vacuum the peptide-resin mixture was washed with ether (2.times.15 ml) on a sintered glass filter to remove anisole and the **peptide** extracted out with **dilute** acid. The acetic acid washings were combined, **diluted** with **water** and **lyophilized** to yield the crude **peptide** (415 mg).

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=> s l3 and cetrorelix
             4 CETRORELIX
L4           0 L3 AND CETRORELIX

=> s l3 and bombesin
           194 BOMBESIN
L5           0 L3 AND BOMBESIN

=> s l3 and somatostatin
          1017 SOMATOSTATIN
L6           5 L3 AND SOMATOSTATIN

=> s protirelin
L7          13 PROTIRELIN

=> s l3 and l7
L8           0 L3 AND L7

=> d pn l3 1-
US PAT NO:     5,157,019 [IMAGE AVAILABLE]          L3: 1 of 27
US PAT NO:     4,908,475 [IMAGE AVAILABLE]          L3: 2 of 27
US PAT NO:     4,826,813 [IMAGE AVAILABLE]          L3: 3 of 27
US PAT NO:     4,810,778 [IMAGE AVAILABLE]          L3: 4 of 27
US PAT NO:     4,760,052 [IMAGE AVAILABLE]          L3: 5 of 27
US PAT NO:     4,711,877 [IMAGE AVAILABLE]          L3: 6 of 27
US PAT NO:     4,705,778 [IMAGE AVAILABLE]          L3: 7 of 27
US PAT NO:     4,684,622 [IMAGE AVAILABLE]          L3: 8 of 27
US PAT NO:     4,643,988 [IMAGE AVAILABLE]          L3: 9 of 27
US PAT NO:     4,626,524 [IMAGE AVAILABLE]          L3: 10 of 27
US PAT NO:     4,624,943 [IMAGE AVAILABLE]          L3: 11 of 27
US PAT NO:     4,599,324 [IMAGE AVAILABLE]          L3: 12 of 27
US PAT NO:     4,587,045 [IMAGE AVAILABLE]          L3: 13 of 27
US PAT NO:     4,560,505 [IMAGE AVAILABLE]          L3: 14 of 27
US PAT NO:     4,543,349 [IMAGE AVAILABLE]          L3: 15 of 27
US PAT NO:     4,542,124 [IMAGE AVAILABLE]          L3: 16 of 27
US PAT NO:     4,444,682 [IMAGE AVAILABLE]          L3: 17 of 27
US PAT NO:     4,427,660 [IMAGE AVAILABLE]          L3: 18 of 27
US PAT NO:     4,372,884 [IMAGE AVAILABLE]          L3: 19 of 27
US PAT NO:     RE 30,548 [IMAGE AVAILABLE]          L3: 20 of 27
US PAT NO:     4,211,693 [IMAGE AVAILABLE]          L3: 21 of 27
US PAT NO:     4,148,787 [IMAGE AVAILABLE]          L3: 22 of 27
US PAT NO:     4,133,782 [IMAGE AVAILABLE]          L3: 23 of 27
US PAT NO:     4,105,603 [IMAGE AVAILABLE]          L3: 24 of 27
US PAT NO:     4,083,967 [IMAGE AVAILABLE]          L3: 25 of 27
US PAT NO:     3,929,756 [IMAGE AVAILABLE]          L3: 26 of 27
US PAT NO:     3,912,711 [IMAGE AVAILABLE]          L3: 27 of 27
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=> d pn l6 1-
US PAT NO:      4,372,884 [IMAGE AVAILABLE]          L6: 1 of 5
US PAT NO:      RE 30,548 [IMAGE AVAILABLE]          L6: 2 of 5
US PAT NO:      4,211,693 [IMAGE AVAILABLE]          L6: 3 of 5
US PAT NO:      4,133,782 [IMAGE AVAILABLE]          L6: 4 of 5
US PAT NO:      4,105,603 [IMAGE AVAILABLE]          L6: 5 of 5

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 SESSION WILL BE HELD FOR 30 MINUTES

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